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Stereoselective Preparation and Stereochemical Behaviour of Organozinc and Organolithium Reagents

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Stephanie Seel

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Seel, S., Dagousset, G., Thaler, T., Frischmuth, A., Karaghiosoff, K., Zipse, H. & Knochel, P. Preparation of stereodefined secondary alkyllithiums. *Chem. Eur. J., accepted.*

TO MY PARENTS

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Abbreviations

Ac	acetyl	h	hour
AcOH	acetic acid	HRMS	high resolution mass spectroscopy
aq.	aqueous		
Ar	aryl	*i*Pr	*iso*-propyl
Boc	*tert*-butoxycarbonyl	IR	infra-red
br	broad	*J*	coupling constant (NMR)
Bu	butyl	LDA	lithium diisopropylamide
*n*Bu	*n*-butyl	m	multiplet
*t*Bu	*t*-butyl	M	molarity
calc.	calculated	*m*	*meta*
conc.	concentrated	Me	methyl
*c*Hex	cyclohexyl	Met	metal
d	doublet	min	minute
δ	chemical shifts in parts per million	mmol	millimole
		M.p.	melting point
dba	*trans,trans*-dibenzylideneacetone	MS	mass spectroscopy
		NMI	*N*-methylimidazole
DCC	*N,N'*-dicyclohexyl-carbodiimide	NMR	nuclear magnetic resonance
		o	*ortho*
DFT	density functional theory	*p*	*para*
DMF	*N,N*-dimethylformamide	PG	protecting group
DMAP	4-(dimethylamino)pyridine	Ph	phenyl
DMSO	dimethyl sulfoxide	q	quartet
E	electrophile	R	organic substituents
EI	electron ionization	rt	room temperature
ESI	electrospray ionization	RuPhos	dicyclohexyl(2’,6’-diisopropoxy-[1,1’-biphenyl]-2-yl)phosphine
equiv.	equivalent		
Et	ethyl		
FG	functional group	s	singulet
GC	gas chromatography	sat.	saturated

SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylene-diamine
TMPP	tris(2,4,6-trimethoxyphenyl)-phosphine
TMS	trimethylsilyl
TP	typical procedure
Ts	4-toluenesulfonyl

A. Introduction

1. Overview

Due to an ever increasing demand of more complex molecular structures for the use in pharmaceutical and agrochemical industries, there is a high need for the development of novel, more efficient and, especially, more stereoselective synthetic methods.[1] Thereby, one of the most important synthetic challenges is the control of the stereochemical information in a molecular framework.[2] This can either be implemented by the use of stereoselective functionalizations making use of a chiral catalyst or auxiliary, as well as the stereogenic bias in a molecule or by the stoichiometric use of stereodefined reagents.[2] Due to their superior reactivities and their versatile applicability, organometallic reagents are especially suitable and a considerable amount of effort has been put into the development of novel methods for the generation of stereodefined carbon-metal bonds using a wide variety of synthetic approaches.[3]

2. Stereoselective Preparation of Organometallic Reagents

2.1. Preparation of Stereodefined Carbon-Lithium Bonds

Stereomeric organolithium compounds featuring a stereodefined carbon-lithium bond have been most studied.[4] However, due to the low configurational stability of the C-Li bond with its high ionic character these studies were mostly restricted to stabilized reagents, such as α-heteroatom substituted alkyl-,[5] benzylic[6] or allylic organolithiums.[7] Moreover, these

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[2] a) *Asymmetric synthesis - The Essentials* (Eds.: M. Christmann, S. Bräse), Wiley-VCH, **2007**; b) A. G. O'Brien, A. G. Recent advances in acyclic stereocontrol. *Tetrahedron* **67**, 9639-9667 (2011).

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[4] a) *Topics in Stereochemistry - Stereochemical Aspects of Organolithium Compounds* (R. E. Gawley, J. S. Siegel), *Vol. 26*, VHCA, Wiley-VCH, **2010**; b) Basu, A. & Thayumanavan, S. Configurational stability and transfer of stereochemical information in the reactions of enantioenriched organolithium reagents. *Angew. Chem. Int. Ed.* **41**, 716-738 (2002).

[5] a) Cohen, T. & Lin, M.-T. Two flask preparation of α-lithio cyclic ethers from γ- and δ-lactones. Reductive lithiation as a route, via radical intermediates, to axial 2-lithiotetrahydropyrans and their equilibration to the equatorial isomers. *J. Am. Chem. Soc.* **106**, 1130-1131 (1984); b) Still, W. C. & Sreekumar, C. α-Alkoxyorganolithium reagents, a new class of configurationally stable carbanions for organic synthesis. *J. Am. Chem. Soc.* **102**, 1201-1202 (1980); c) Hoppe, D., Hintze, F. & Tebben, P. Chiral lithium-1-oxyalkanides by asymmetric deprotonation; enantioselective synthesis of 2-hydroxyalkanoic acids and secondary alkanols. *Angew.Chem. Int. Ed. Engl.* **29**, 1422-1424 (1990); d) Rychnovsky, S. D. & Mickus, D. E. Preparation of 2-

organolithium reagents can be accessed more easily via conventional stereoselective deprotonation reactions featuring chiral amine ligands, such as (-)-sparteine (**1**).[4b,7a] Thus, *Curtis* and *Beak* have reported on the stereoselective generation of the configurationally stable benzylic and allylic organolithium species **2** and **3** via asymmetric deprotonation mediated by **1** (Scheme 1).[8]

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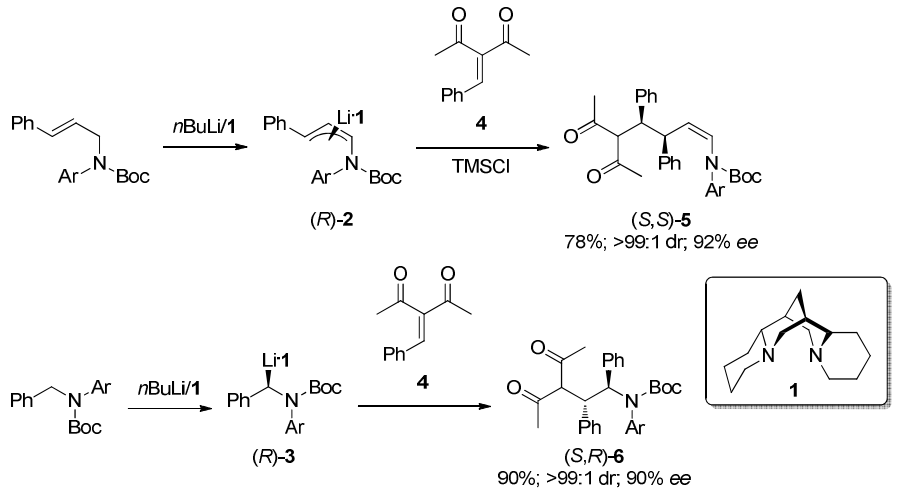
lithiotetrahydropyrans: Kinetic and thermodynamic generation of alkyllithium reagents. *Tetrahedron Lett.* **30**, 3011-3014 (1989); e) Rychnovsky, S. D., Buckmelter, A. J., Dahanukar, V. H. & Skalitzky, D. J. Synthesis, equilibration, and coupling of 4-lithio-1,3-dioxanes: synthons for syn- and anti-1,3-diols. *J. Org. Chem.* **64**, 6849-6860 (1999); f) Kapeller, D. C., Brecker, L. & Hammerschmidt, F. Configurational stability of oxymethyllithiums as intermediates in intramolecular rearrangements. *Chem. Eur. J.* **13**, 9582-9588 (2007); g) Kapeller, D. C. & Hammerschmidt, F. Enantiopure chiral (2,4,6-triisopropylbenzoyl)oxy-[D_1]methyllithium: configurational stability, reactions, and mechanistic studies. *J. Org. Chem.* **74**, 2380-2388 (2009); h) Schlosser, M. & Limat, D. Sparteine-mediated α-lithiation of *N*-BOC-*N*-methylbenzylamine: rapid racemization and subsequent deracemization. *J. Am. Chem. Soc.* **117**, 12342-12343 (1995); i) Serino, C., Stehle, N., Park, Y. S., Florio, S. & Beak, P. Asymmetric syntheses of N-Boc 2-substituted pyrrolidines and piperidines by intramolecular cyclization. *J. Org. Chem.* **64**, 1160-1165 (1999); j) Gawley, R. E. & Zhang, Q. 2-Lithio-*N*-methylpiperidine and 2-lithio-*N*-methylpyrrolidine: configurationally and chemically stable unchelated α-aminoorganolithiums. *J. Am. Chem. Soc.* **115**, 7515-7516 (1993); k) Coldham, I., Dufour, S., Haxell, T. F. N., Patel, J. J. & Sanchez-Jimenez, G. Dynamic thermodynamic and dynamic kinetic resolution of 2-lithiopyrrolidines. *J. Am. Chem. Soc.* **128**, 10943-10951 (2006); l) Kapeller, D. C. & Hammerschmidt, F. Preparation of enantiopure chiral amino-[D_1]methyllithium compounds and determination of their micro- and macroscopic configurational stabilities. *Chem. Eur. J.* **15**, 5729-5739 (2009); m) Hoffmann, R. W., Dress, R. K., Ruhland, T. & Wenzel, A. Enantiomerization of α-thio-, α-seleno-, and α-telluro-substituted alkyllithium compounds; kinetic and mechanistic studies. *Chem. Ber.* **128**, 861- 870 (1995); n) O'Brien, P. & Warren, S. Investigation of the configurational stability of lithiated phosphine oxides using diastereomerically pure and enantiomerically enriched phosphine oxides. *J. Chem. Soc., Perkin Trans. **1***, 2567- 2573 (1996); o) Hoffmann, R. W., Ruhland, T. & Bewersdorf, M. On the configurational stability of α-bromo-alkyllithium compounds. *J. Chem. Soc., Chem. Commun.*, 195-196 (1991); p) Kapeller, D. C. & Hammerschmidt, F. Preparation and configurational stability of chiral chloro-[D_1]methyllithiums of 98% enantiomeric excess. *J. Am. Chem. Soc.* **130**, 2329- 2335 (2008).

[6] a) Lefranc, J., Fournier, A. M., Mingat, G., Herbert, S., Marcelli, T. & Clayden, J. Intramolecular vinylation of secondary and tertiary organolithiums. *J. Am. Chem. Soc.* **134**, 7286-7289 (2012); b) Clayden, J., Helliwell, M., Pink, J. H. & Westlund, N. Stereospecificity and stereoselectivity in electrophilic substitution reactions of non-α-heterosubstituted organolithiums and stannanes: a rotationally restricted amide as an internal stereochemical marker. *J. Am. Chem. Soc.* **123**, 12449-12457 (2001); c) Hoffmann, R. W., Rühl, T., Chemla, F. & Zahneisen, T. On the configurational stability of α-methylbenzyllithium. *Liebigs. Ann. Chem.*, 719-724 (1992); d) Peoples, P. R. & Grutzner, J. B. Structure of the 7-phenylnorbornyl carbanion. A pyramidal organolithium and planar organopotassium. *J. Am. Chem. Soc.* **102**, 4709-4715 (1980); e) Prat, L., Mojovic, L., Levacher, V., Dupas, G., Quéguiner, G. & Bourguignon, J. Deracemization of diarylmethanes via lateral lithiation-protonation sequences by means of sparteine. *Tetrahedron: Asymmetry* **9**, 2509-2516 (1998); f) Hoppe, I., Marsch, M., Harms, K., Boche, G. & Hoppe, D. Generation of enantiomerically enriched lithium indenides by means of (-)-sparteine: structure, stereoselective substitution and solvent effects. *Angew. Chem. Int. Ed. Engl.* **34**, 2158-2160 (1995); g) Curtis, M. D. & Beak, P. Asymmetric carbon-carbon bond formation in Michael reactions: conjugate addition reactions of configurationally stable benzylic and allylic organolithium species *J. Org. Chem.* **64**, 2996-2997 (1999).

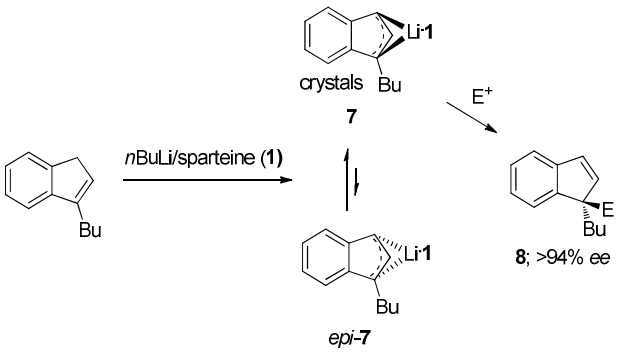
[7] a) Hoppe, D. & Hense, T. Enantioselective synthesis with lithium/(-)-sparteine carbanion pairs. *Angew. Chem. Int. Ed. Engl.* **36**, 2282-2316 (1997); b) Hoppe, D. α-Metallated O-2-alkenyl carbamates: synthetic equivalents of chiral homoenolates and materials for asymmetric homoaldol reaction. *Synthesis*, 43-55 (2009); c) Hoppe, I., Marsch, M., Harms, K., Boche, G. & Hoppe, D. Generation of enantiomerically enriched lithium indenides by means of (-)-sparteine: structure, stereoselective substitution and solvent effects. *Angew. Chem. Int. Ed. Engl.* **34**, 2158-2160 (1995); d) Curtis, M. D. & Beak, P. Asymmetric carbon-carbon bond formation in Michael reactions: conjugate addition reactions of configurationally stable benzylic and allylic organolithium species *J. Org. Chem.* **64**, 2996-2997 (1999).

[8] Curtis, M. D. & Beak, P. Asymmetric carbon-carbon bond formation in Michael reactions: conjugate addition reactions of configurationally stable benzylic and allylic organolithium species. *J. Org. Chem.* **64**, 2996-2997 (1999).



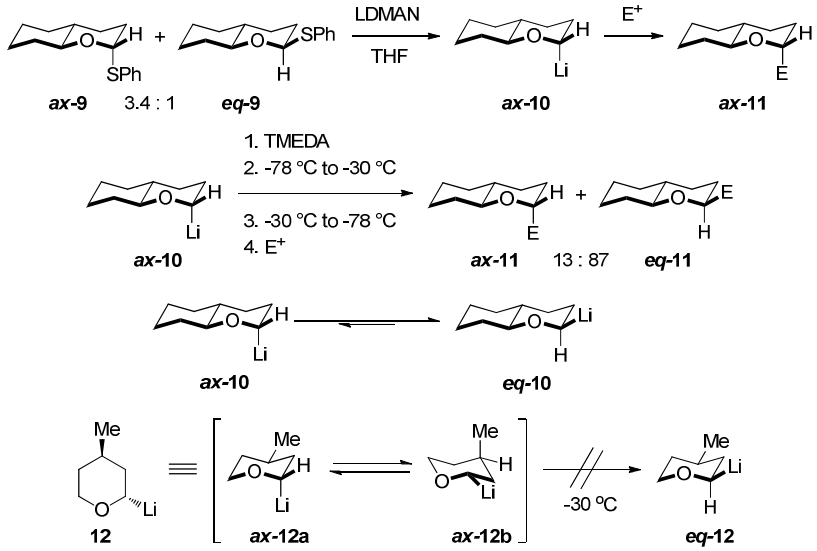
Scheme 1: Generation of chiral allylic and benzylic organolithium species via (-)-sparteine-mediated enantioselective deprotonation.

Their conjugate addition to benzylideneacetylacetone (**4**) provided the adducts (*S*,*S*)-**5** and (*S*,*R*)-**6** with superior regio-, diastereo- and enantioselectivities. *Hoppe et al.* also showed that (-)-sparteine (**1**) can be used to selectively stabilize the non-heteroatom α-substituted chiral lithium indenide **7** by crystallization leading after quenching with electrophiles to the respective enantioenriched products of type **8** (Scheme 2).[7c]



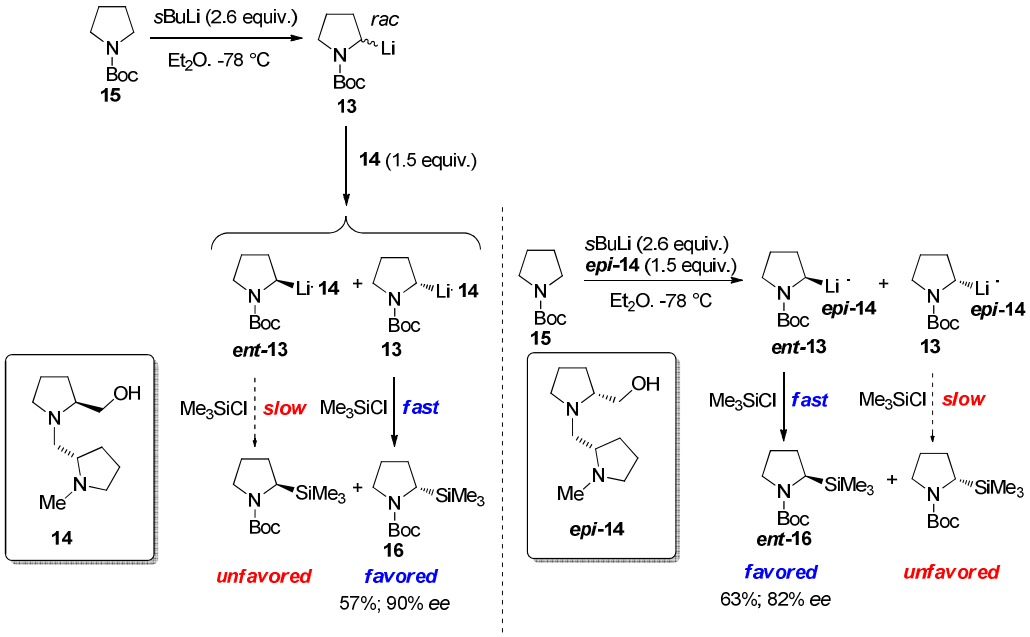
Scheme 2: Generation of chiral α-substituted lithium indenide **7** by crystallization with (-)-sparteine (**1**).

Cohen and *Lin* observed an interesting phenomenon based on both the configurational instability of the highly anionic C-Li bond and the stereochemical bias in substituted lithiopyrans.[5a] Thus, reductive lithiation of the conformationally locked thioether **9** (*axial*:*equatorial*= 3.4:1) using lithium 1-(dimethylamino)napthalenide (**LDMAN**) exclusively furnished axially substituted organolithium compound ***ax*-10** (Scheme 3).



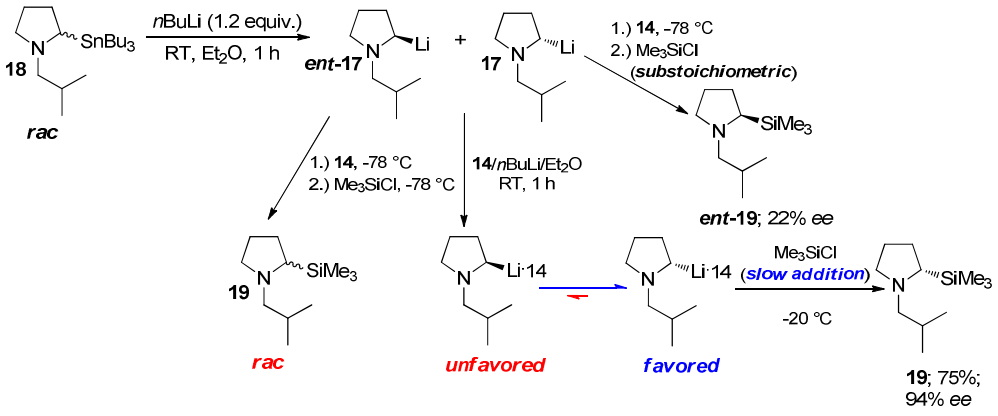
Scheme 3: Stereospecific generation of lithiofurans via reductive lithiation of thioethers and the different stereochemical stabilities of the conformationally locked lithium reagent ***ax*-10** and flexible **12**.

Quenching with benzaldehyde (PhCHO), D_2O or CD_3CO_2D furnished products of type ***ax*-11** with extraordinarily high selectivity. Remarkably, when ***ax*-10** was warmed to -30 °C in the presence of chelating TMEDA and cooled back to -78 °C, the equatorially substituted products of type ***eq*-11** were obtained preferentially. This showed that ***ax*-10** had equilibrated into the more stable ***eq*-10** via inversion of the C-Li bond. This thermodynamic control could, however, not be applied to the 3-methyl-substituted 2-lithiopyran **12**. The authors suggested that the flexibility of **12** is responsible for the lacking epimerization of the C-Li bond. Thus, ***ax*-12a** in which the Li occupies the axial position can easily undergo a ring flip placing the Li moiety in the more stable equatorial position (***ax*-12b**) thus rendering an epimerization (formation of ***eq*-12**) as observed in the conformationally locked lithiopyran **10** unnecessary for the C-Li bond to occupy its thermodynamically preferred position. *Coldham et al.* also made use of the configurational instability of organolithium compounds. They showed that *N*-Boc-2-lithiopyrrolidine (**13**) can be subjected to a dynamic kinetic resolution (DKR) process in the presence of the diastereomeric chiral aminoalcohol-ligands **14** and ***epi*-14** (Scheme 4).[5k]



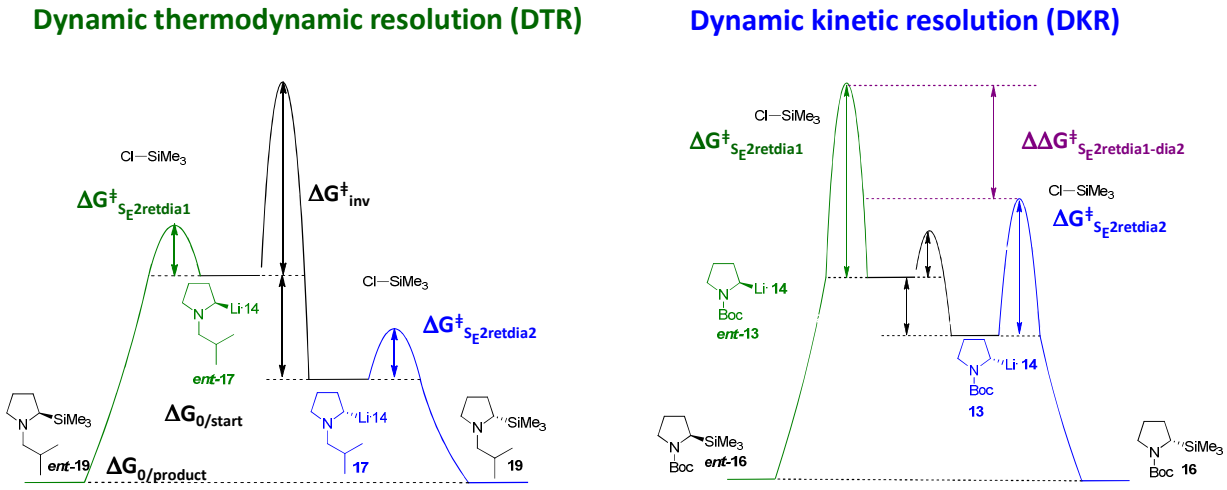
Scheme 4: Dynamic kinetic resolution (*DKR*) in *N*-Boc-2-lithiopyrrolidine (**13** and ***ent*-13**) using the chiral aminoalcohol-ligands **14** and ***epi*-14**.

Thus, deprotonation of *N*-Boc-pyrrolidine (**15**) using *s*BuLi in the presence of a chiral ligand led to the respective complexes between **13** and enantiomeric ***ent*-13** with **14** or ***epi*-14**. The complex **13•14** reacted faster with Me_3SiCl as electrophile than the diastereomeric complex ***ent*-13•14** leading to the chiral silane **16** with high enantioselectivity. When ***epi*-14** was employed as ligand the ensuing complex ***ent*-13•*epi*-14** reacted preferably giving a highly selective access to the opposite enantiomer of **16** (***ent*-16**) upon quenching with Me_3SiCl. Another interesting dynamic resolution process based on thermodynamic control (compare Scheme 3) was observed by *Coldham et al.* for the *N-iso*-butyl-substituted lithiopyrrolidines **17** and ***ent*-17** in conjunction with the chiral aminoalcohol ligand **14** (Scheme 5).



Scheme 5: Dynamic thermodynamic resolution (*DTR*) in *N-iso*-butyl-substituted 2-lithiopyrrolidine (**17** and ***ent*-17**) using the chiral amino alcohol ligands **14**.

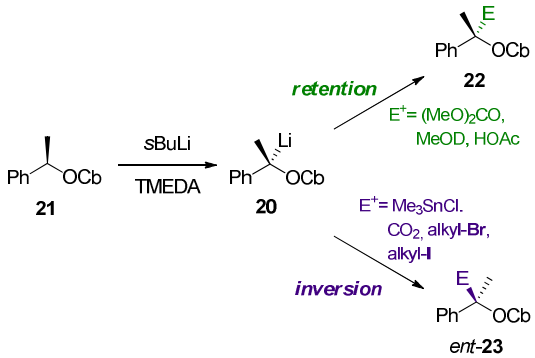
Sn-Li exchange on stannane **18** led to the lithium species **17** and ***ent*-17**. At -78 °C addition of the chiral ligand **14** leading to the formation of the complexes **17•14** and ***ent*-17•14** and subsequent quenching with Me_3SiCl gave only racemic product (**19**). When the Sn-Li exchange and addition of the chiral ligand **14** was performed at ambient temperature quenching with Me_3SiCl furnished **19** with high enantioselectivity (94% *ee*). Interestingly, quenching with a substoichiometric amount of Me_3SiCl at -78 °C gave the product with low selectivity and a preference for the opposite enantiomer (***ent*-19**). This hints at a dynamic thermodynamic resolution process in which the less stable complex ***ent*-17•14** equilibrates into the diastereomeric complex **17•14**. The energy diagrams for the dynamic thermodynamic (Scheme 5) and the dynamic kinetic resolution processes (Scheme 4) are depicted in Scheme 6.



Scheme 6: Representative energy schemes for the dynamic thermodynamic resolution (DTR) and the dynamic kinetic resolution of lithiopyrrolidines with chiral ligands.

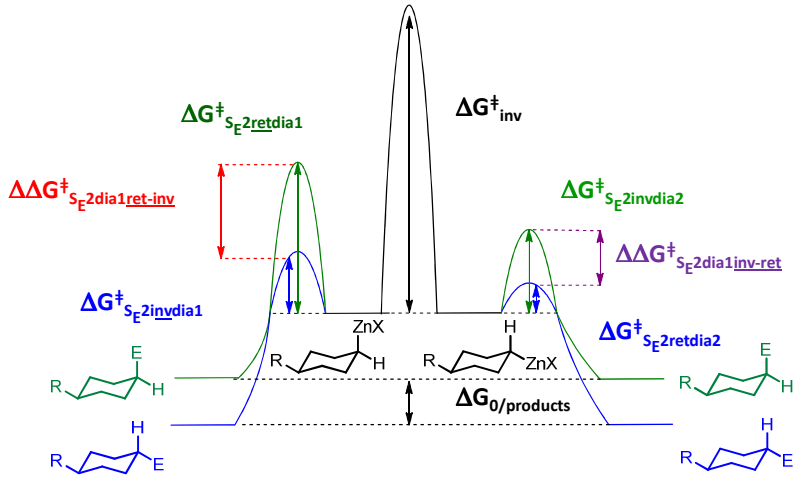
In the latter, the difference in activation energies ($\Delta\Delta G^{\neq}$) for the quenching reactions determines the overall stereoselectivity of the process with a low activation energy barrier for equilibration between **13•14** and ***ent*-13•14**. In the former, the difference in ground state energies (ΔG^0) between the diastereomeric complexes **17•14** and ***ent*-17•14** is responsible for the stereochemical outcome. A relatively high activation barrier for equilibration between **17•14** and ***ent*-17•14** leads to a stable equilibrium between those complexes at lower temperatures (quenching temperature: -20 °C). Interestingly, the stereochemical paths of S_E2 reactions of chiral organolithium compounds are not uniform for all electrophiles. Thus, *Hoppe* and *Hammerschmidt* could show that the nature of the respective electrophiles

determined the stereochemical outcome of the quenching of the tertiary benzylic Li-reagent **20**, which was derived from **21** via deprotonation using *s*BuLi and TMEDA (Scheme 7).[9]



Scheme 7: Electrophile-dependent stereochemical outcome in the quenching of the chiral benzylic lithium reagent **20**.

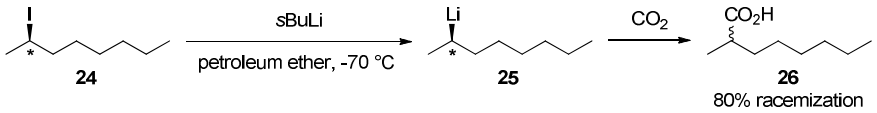
Thus, electrophiles like MeOD, HOAc and $(MeO)_2CO$ furnish the respective products of type **22** with retention of stereoconfiguration, whereas invertive substitution is observed with Me_3SnCl, CO_2, alkyl bromides and iodides leading to products of type ***ent*-23**.



Scheme 8: Hypothetical scenario with different activation barriers for invertive and retentive quenching for two distinct diastereomeric organozinc reagents (in this simplified scheme same ground state energies are assumed for the organometallic diastereomeric reagents and diastereomeric quenching products; this does not necessarily need to be the case).

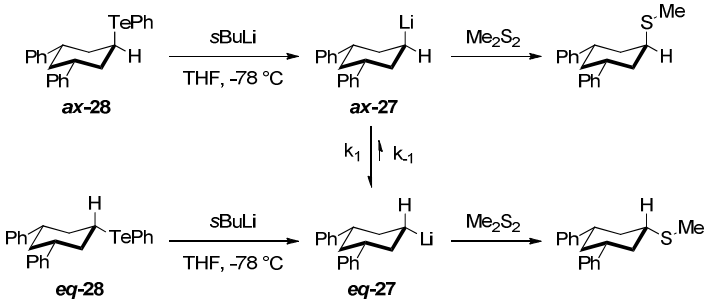
[9] a) Hoppe, D., Carstens, A. & Krämer, T. Generation of a configurationally stable chiral benzyllithium derivative, and the capricious stereochemistry of its electrophilic substitution. *Angew. Chem. Int. Ed. Engl.* **29**, 1424-1425 (1990); b) Carstens, A. & Hoppe D. Generation of a configurationally stable, enantioenriched α-oxy-α-methylbenzyIlithium: stereodivergence of its electrophilic substitution. *Tetrahedron* **50**, 6097-6108 (1994); c) Hammerschmidt, F., Hanninger, A. & Völlenkle, H. Proof of inversion of configuration on stannylation of a configurationally stable, tertiary benzyllithium compound from a single-crystal X-ray structure analysis. *Chem. Eur. J.* **3**, 1728-1732 (1997).

Therefore, a scenario in which distinct kinetic preferences in the quenching reactions for diastereomeric organometallics in which one reacts with retention and the other with inversion of the C-metal bond is also conceivable but has not yet been reported in the literature so far. Scheme 8 shows an energy diagram for such a hypothetical scenario in which distinct activation energy barriers for the retentive and invertive substitution processes lead to different stereochemical outcomes. The stereoselective generation of unstabilized secondary alkyllithium reagents has been far less studied. An early report by *Letsinger* featured an I-Li exchange on (-)-2-iodooctane (**24**) at -70 °C leading to stereodefined 1-methylheptyllithium (**25**) which was quenched with CO_2 to give the carbonic acid **26** with 80% racemization (Scheme 9).[10]



Scheme 9: I-Li exchange on enantiopure (-)-2-iodooctane and quenching with CO_2 at -70 °C goes along with 80% racemization.

Reich et al. reported on the stereoselective generation of the diastereomeric cyclohexyllithium compounds ***ax*-27** and ***eq*-27** via Te-Li exchange on tellurides ***ax*-28** and ***eq*-28** (Scheme 10).[11] The influence of chelators such as TMEDA and PMDTA and lithium iodide salt on the configurational stability of ***ax*-27** which tends to equilibrate into the more stable ***eq*-27** was examined**.**

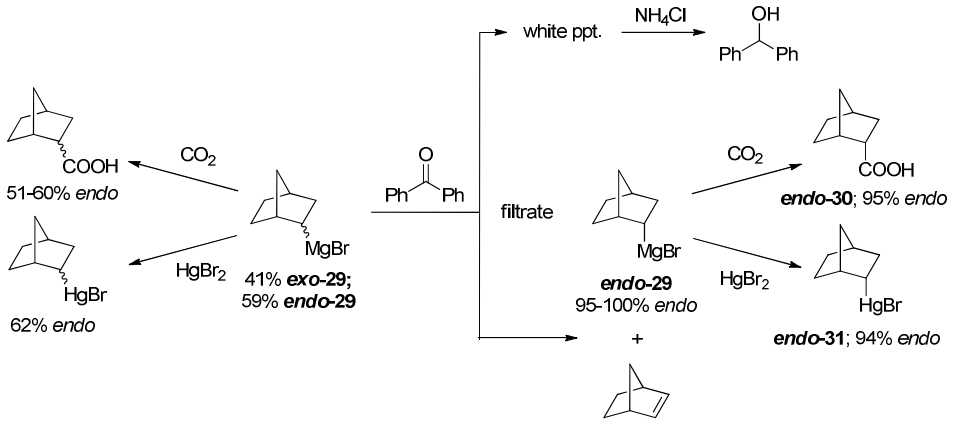


Scheme 10: Te-Li exchange on stereodefined cyclohexyl tellurides ***ax*-28** and ***eq*-28** proceeds with retention of stereoconfiguration.

[10] Letsinger, R. L. Formation of optically active 1-methylheptyllithium. *J. Am. Chem. Soc.* **72**, 4842 (1950).
[11] Reich, H. J., Medina, M. A. & Bowe, M. D. Stereochemistry of a cyclohexyllithium reagent. A case of higher configurational stability in strongly coordinating media. *J. Am. Chem Soc.* **114**, 11003-11004 (1992).

2.2. Preparation of Stereodefined Carbon-Magnesium Bonds

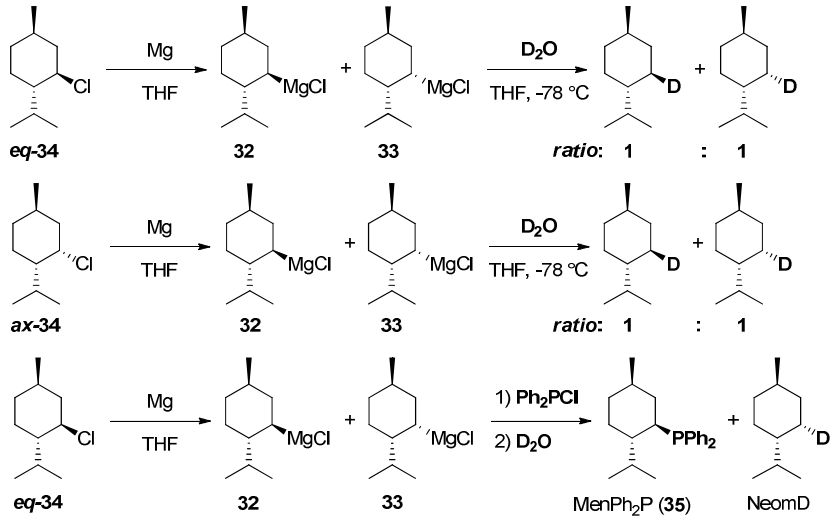
Stereodefined Grignard reagents have been much less studied than their organolithium counterparts. *Jensen* and *Nakamaye* reported on the stereoselective generation of *endo*-norbornylmagnesium bromide (***endo*-29**) via a kinetic resolution process already as early as 1966.[12] They used the greater reactivity of ***exo*-29** towards the reduction of benzophenone to selectively remove it (Scheme 11).



Scheme 11: Kinetic resolution of the diastereomeric norbornylmagnesium reagents ***exo*-29** and ***endo*-29**.

The remaining ***endo*-29** was studied by NMR and trapping experiments with $HgBr_2$ and CO_2 gave the respective *endo*-products ***endo*-30** and ***endo*-31** stereospecifically with retention of configuration. In accordance with the results of *Whitesides* and *Roberts*[13] only a very slow interconversion from ***endo*-29** to ***exo*-29** was observed showing the relatively high configurational stability of these bicyclic secondary alkyl Grignard reagents. The (-)-menthyl-/neomenthyl Grignard reagents **32** and **33** represent the most extensively studied chiral organomagnesium reagents (Scheme 12).[14]

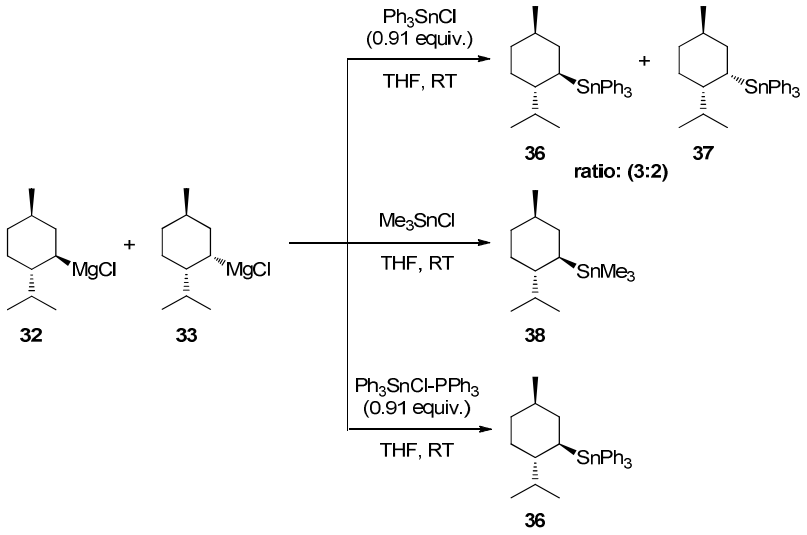
[12] Jensen, F. R. & Nakamaye, K. L. Preparation of geometrically isomeric Grignard reagents and the stereochemical courses of their reactions. *J. Am. Chem. Soc.* **88**, 3437-3438 (1966).
[13] Whitesides, G. M. & Roberts, J. D. Nuclear magnetic resonance spectroscopy. The configurational stability of primary Grignard reagents. *J. Am. Chem. Soc.* **87**, 4878-4888 (1965).
[14] Beckmann, J., Dakternieks, D., Dräger, M. & Duthie, A. New insights into the classic chiral Grignard reagent (1*R*,2*S*,5*R*)-menthylmagnesium chloride. *Angew. Chem. Int. Ed. Engl.* **45**, 6509-6512 (2006).



Scheme 12: Mg-insertion in either menthyl chloride (***eq*-34**) or neomenthyl chloride (***ax*-34**) results in a 1:1-mixture of the diastereomeric Grignard reagents **32** and **33**; **32** can be selectively trapped using Ph_2PCl.

Originally, it was believed that the insertion of Mg metal into (-)-menthyl chloride (***eq*-34**) would exclusively lead to the stereodefined **33**, since quenching of the resulting Grignard reagent(s) with Ph_2PCl only gave equatorially substituted diastereomeric phosphine **35**.[15] A more recent investigation by *Beckmann*, *Dakternieks* and *Duthie* showed that, after Mg-insertion into **34**, a 1:1-mixture of diastereomeric **32** and **33** ensues, which was proven by quenching the mixture with D_2O.[15] The same ratio was found when Mg-insertion was performed on the diastereomeric neomenthyl chloride (***ax*-34**) The reaction of this mixture with 0.5 equiv. of Ph_2PCl was reported to result in a kinetic resolution similar to the one shown in Scheme 11 where the more reactive and more Lewis-acidic **32** was selectively quenched and **33** remained in solution, as proven by quenching with D_2O. Interestingly, the stereochemical outcome of the quenching reactions of the **32**/**33** mixture is highly dependent on the nature of the electrophile. Thus, *Dakternieks et al*. observed a 3:2-mixture of the diastereomeric stannanes **36** and **37** upon quenching with Ph_3SnCl,[16] whereas the reaction with Me_3SnCl was reported by *Schumann et al.* to give exclusively the equatorially substituted stannane **38** (Scheme 13).[17]

[15] Tanaka, M. & Ogata, I. A novel route to menthyldiphenylphosphine. *Bull. Chem. Soc. Jpn.* **48**, 1094 (1975).
[16] Dakternieks, D., Dunn, K. & Henry, D. J. Organostannanes derived from (-)-menthol: controlling stereochemistry during the preparation of (1*R*,2*S*,5*R*)-menthyldiphenyltin hydride an bis((1*R*,2*S*,5*R*)-menthyl)phenyltin hydride. *Organometallics* **18**, 3342-3347 (1999).
[17] Schumann, H., Wassermann, B. C. & Hahn, F. E. Synthesis and characterization of chiral (-)-menthyltin (4) compounds. X-ray structure of tert-butyl-8-(dimethylamino)naphthyl-(-)-menthyltin hydride. *Organometallics* **11**, 2803-2811 (1992).

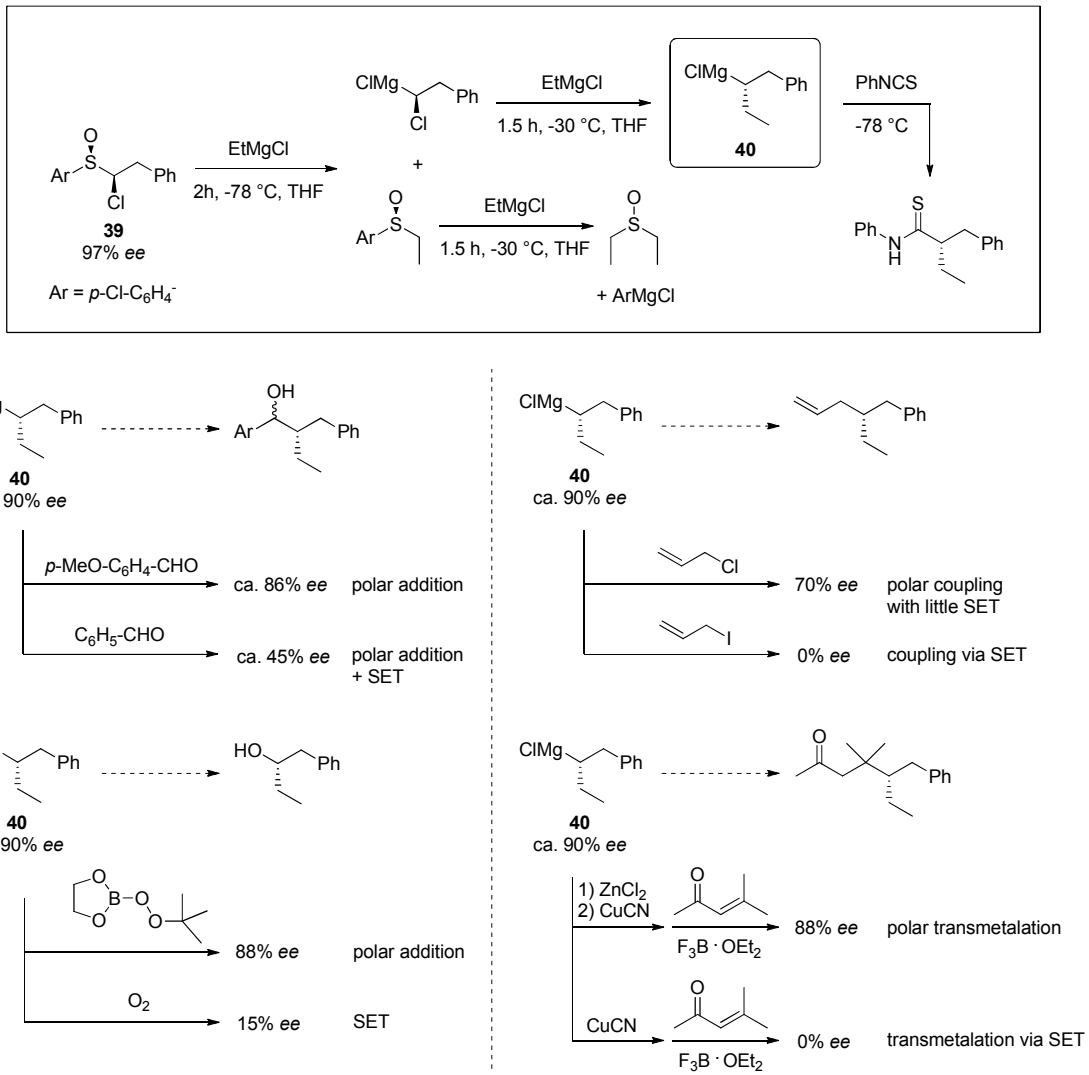


Scheme 13: Quenching of the diastereomeric Grignard reagents **32** and **33** with different organotin chlorides leading to distinct stereochemical outcomes.

The addition of Lewis-bases, such as Ph_3P, to Ph_3SnCl prior to the addition of the **32**/**33** mixture restored selectivity presumably due to a decreased Lewis-acidity of the Ph_3SnCl-PPh_3 complex. At that time, the **32**/**33**-mixture was still considered to consist of only **32** and an electrophile-triggered radical epimerization of **32** was proposed.[17] *Hoffmann et al.* developed a general and straightforward access to chiral organomagnesium reagents via a sulfoxide-magnesium exchange/ carbenoid homologation sequence using excess EtMgCl and α-chloro-substituted chiral secondary alkylsulfoxides of type **39**.[18] The resulting chiral organomagnesium reagent **40** was shown to undergo racemization at -10 °C in a first order process with a half-life of only 5 h.[19] **40** was subjected to trapping and transmetalation reactions with different electrophiles (Scheme 14).[19]

[18] a) Hoffmann, R. The quest for chiral Grignard reagents. *Chem. Soc. Rev.* **32**, 225-230 (2003); b) Hoffmann, R. W., Hölzer, B., Knopff, O. & Harms, K. Asymmetric synthesis of a chiral secondary Grignard reagent. *Angew. Chem. Int. Ed.* **39**, 3072-3074 (2000).

[19] a) Hoffmann, R. W., Hölzer, B. & Knopff, O. Amination of Grignard reagents with retention of configuration. *Org. Lett.* **3**, 1945-1948 (2001); b) Hoffmann, R. W. & Hölzer, B. Concerted and stepwise Grignard additions, probed with a chiral Grignard reagent. *Chem. Commun.*, 491-492 (2001); c) Hoffmann, R. W. & Hölzer, B. Stereochemistry of the transmetalation of Grignard reagents to copper (I) and manganese (II). *J. Am. Chem. Soc.* **124**, 4204-4205 (2002); d) Hoffmann, R. W. & Hölzer, B. Kumada–Corriu coupling of Grignard reagents, probed with a chiral Grignard reagent. *Chem. Commun.*, 732-733 (2003).



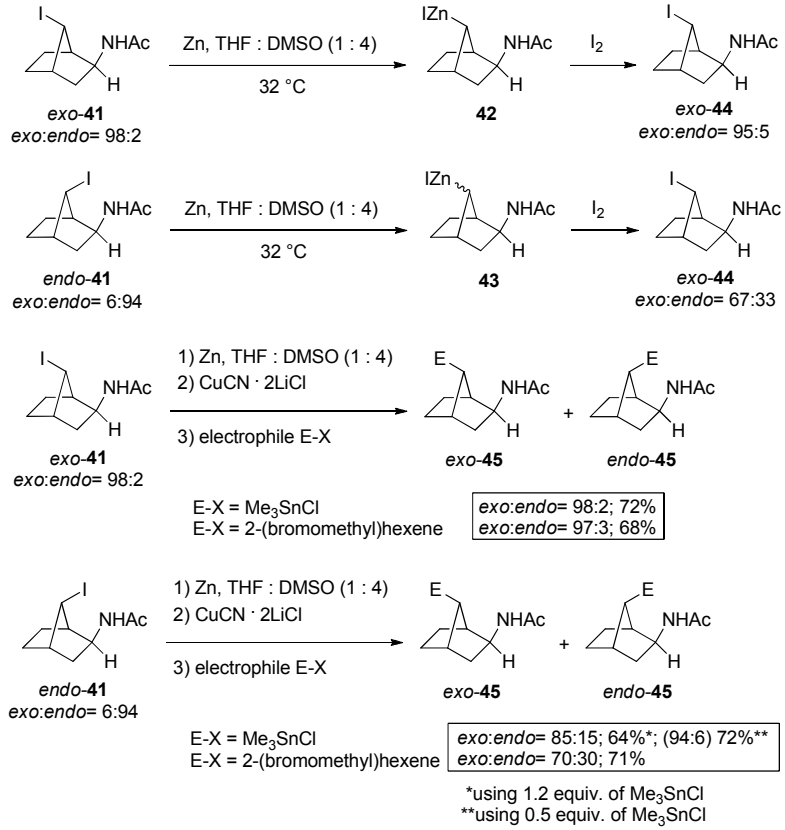
Scheme 14: Enantioselective generation of secondary alkylmagnesium reagents via sulfoxide magnesium exchange and electrophile-dependent stereochemical outcomes.

These experiments showed that the stereochemical outcome highly depends on the nature of the respective electrophile. Whereas retention of the stereoinformation hinted toward polar addition processes, losses in enantiopurity were interpreted to indicate radical single electron transfer (***SET***) processes.

2.3. Preparation of Stereodefined Carbon-Zinc Bonds

Reports on the generation and configurational behaviour of stereodefined organozinc reagents are scarce in the literature. Despite their usefulness for organic synthesis due to their high tolerance towards functional groups and their decreased reactivity relative to the corresponding organo-lithium and -magnesium species, their stereochemical behaviour has

not yet been studied in detail. This may be due to the fact that stereodefined C-Zn bonds are not easy to generate. A first seminal investigation on the stereochemical behaviour of secondary diastereomeric organozinc reagents was published by *Knochel et al.* in 1994.[20] In this article, Zn-insertion was performed on the *endo*- and *exo*-norbornyl iodides ***exo*-41** and ***endo*-41** and the resulting zinc reagents (**42** and **43**) were subjected to quenching with different electrophiles (Scheme 15).

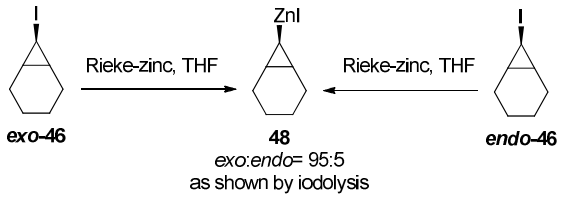


Scheme 15: Stereoselective generation of secondary alkylzinc reagents. A phenomenon of stereoconvergent quenching or of an amide-directed Zn-insertion?

Interestingly, iodolysis of **42** gave the iodide ***exo*-44** with high diastereoselectivity (*exo:endo*= 95:5), whereas quenching of **43** with I_2 led to a 67:33-mixture in favour of ***exo*-44**. From these results it was concluded that the Zn-insertion into ***exo*-41** proceeded stereoselectively to give the stereodefined Zn-reagent **42**, while Zn-insertion into the diastereomeric ***endo*-41** furnished a mixture of *exo-/endo*-configured Zn-reagents. Further quenching reactions using Me_3SnCl and 2-(bromomethyl)hexane confirmed the observed trend. Still, when **43** was trapped, after transmetalation to copper, with Me_3SnCl the stereochemical outcome depended highly on the

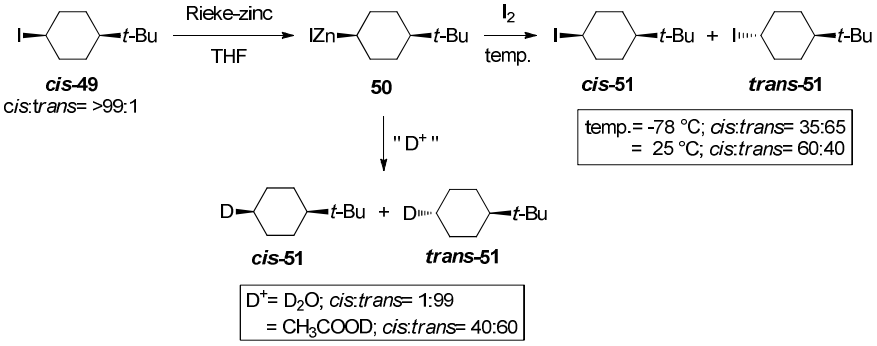
[20] Duddu, R., Eckhardt, M., Furlong, M., Knoess, H. P., Berger, S. & Knochel, P. Preparation and reactivity of chiral β-amido-alkylzinc iodides and related configurationally stable zinc organometallics. *Tetrahedron* **50**, 2415-2432 (1994).

amount of equivalents used. Thus, a 85:15 d.r. in favour of ***exo*-45** was obtained with 1.2 equiv. Me_3SnCl which could be increased to 94:6 with only 0.5 equiv. of Me_3SnCl. Another interesting observation was made, when *exo*- and *endo*-7-iodonorcarane (***exo*-46** and ***endo*-46**) were subjected to Zn-insertion using *Rieke*-zinc (Scheme 16).



Scheme 16: Stereoselective generation of secondary alkylzinc reagents. A phenomenon of stereoconvergent quenching? Zinc-insertion into ***exo*-** and ***endo*-7**-iodonorcarane (***exo*-46** and ***endo*-46**).

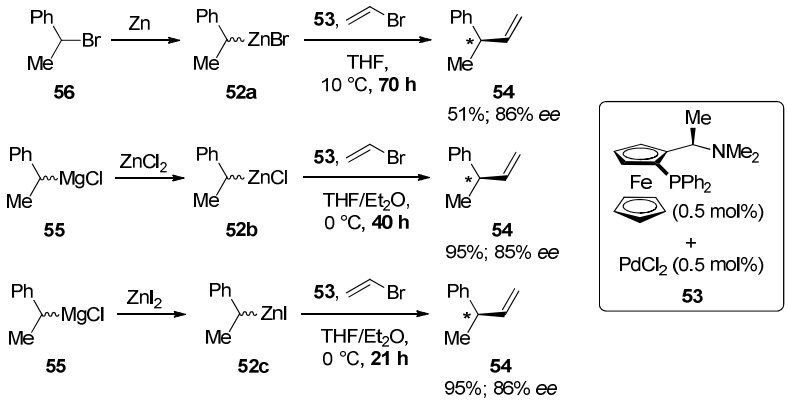
In both cases, after iodolysis an *exo*/*endo* ratio of the resulting iodide (**46**) of 95:5 was obtained. Thus, the stereoselective formation of *exo*-zinc reagent **48** was concluded. When Zn-insertion was performed on *cis*-4-*tert*-butylcyclohexyl iodide **49** using *Rieke*-zinc and the resulting organozinc species **50** was quenched with I_2 the respective organic iodide products (***cis*-51** and ***trans*-51**) were obtained in a 35:65 *cis*:*trans*-ratio at -78 °C and in a 60:40-ratio at 25 °C (Scheme 17).



Scheme 17: Stereoselective generation of secondary alkylzinc reagents? A phenomenon of stereoconvergent quenching? Dependence of the stereoselectivity on reaction conditions and electrophiles.

Trapping of **50** with AcOD resulted in a 60:40-ratio of deuterated products (***cis*-51** and ***trans*-51**). Quenching with D_2O, however, gave almost exlusively ***trans*-51**. These results underlined the influence of reaction conditions on the stereochemical outcome of the quenching reactions. The conclusion that only one Zn-species is formed in the case of **42** and **47** has still to be verified, since the zinc reagent was not directly analyzed spectroscopically. Further insights into the stereochemical behaviour of C-Zn reagents were given by the

enantioselective cross-coupling of the benzylic zinc reagents **52a-c** using a chiral ferrocene-based Pd-catalyst (**53**) by *Hayashi* and *Kumada* (Scheme 18).[21]

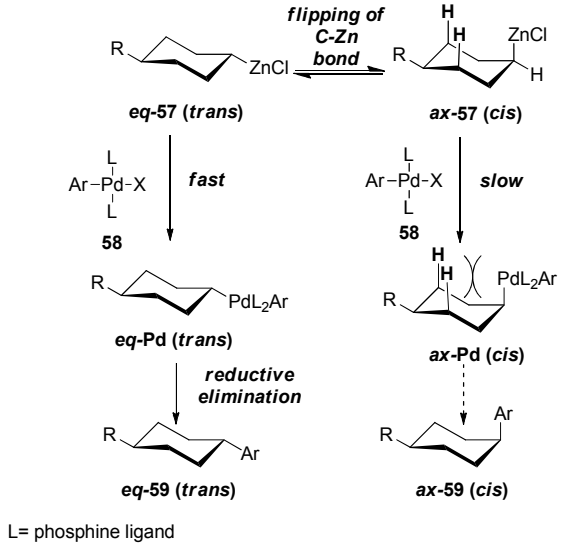


Scheme 18: Enantioselective Pd-catalyzed cross-coupling of secondary alkylzinc reagents **52a-c**.

The racemic zinc reagents **52a-c** were proposed to undergo a dynamic kinetic resolution process in the presence of chiral **53** thus leading to the cross-coupling product **54** with high enantioselectivities.[2a] Thus, the organozinc reagents **52b-c**, which were obtained via transmetalation from the Grignard reagent **55**, reacted much faster and gave higher yields than **52a** which was prepared via Zn-insertion into the benzylic bromide **56**. Such a dynamic kinetic resolution process has also been proposed for the remotely controlled diastereoselective cross-coupling of 3- and 4-substituted cyclohexylzinc reagents (Scheme 19).[22]

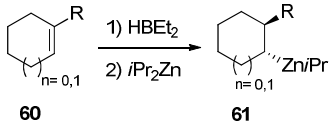
[21] Hayashi, T., Hagihara, T., Katsuro, Y. & Kumada, M. Asymmetric cross-coupling of organozinc reagents with alkenyl bromides catalyzed by a chiral ferrocenylphosphine-palladium complex. *Bull. Chem. Soc. Jpn.* **56**, 363-364 (1983).

[22] Thaler, T., Haag, B., Gavryushin, A., Schober, K., Hartmann, E., Gschwind, R., Zipse, H., Mayer, P. & Knochel, P. Highly diastereoselective Csp^3-Csp^2 Negishi cross-coupling with 1,2-, 1,3- and 1,4-substituted cycloalkylzinc compounds. *Nature Chem.* **2**, 125-130 (2010).



Scheme 19: A DKR mechanism proposed for the stereoconvergent *Negishi* cross-couplings of diastereomeric cyclohexylzinc reagents.

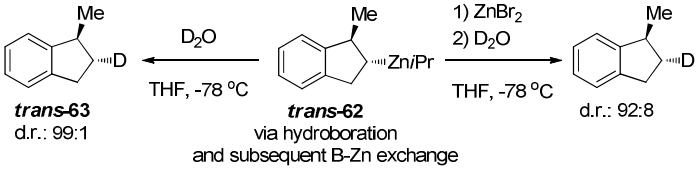
Here, the equatorially substituted cyclohexylzinc reagent ***eq*-57** was assumed to react much faster with the arylpalladium complex **58** than ***ax*-57** thus selectively leading to the thermodynamically favoured all-equatorially substituted products of type ***eq*-59** (transmetalation and reductive elimination were assumed to proceed with rentention of stereoconfiguration). An efficient way for the stereoselective generation of C-Zn bonds was disclosed by *Knochel et al.*: A hydroboration/B-Zn exchange sequence on trisubstituted double-bonds (**60**) leads to the regio- and stereodefined *trans*-configured organozinc reagents of type **61** (Scheme 20).[23]



Scheme 20: Hydroboration/B-Zn exchange sequence for the generation of diastereomerically defined organozinc reagents.

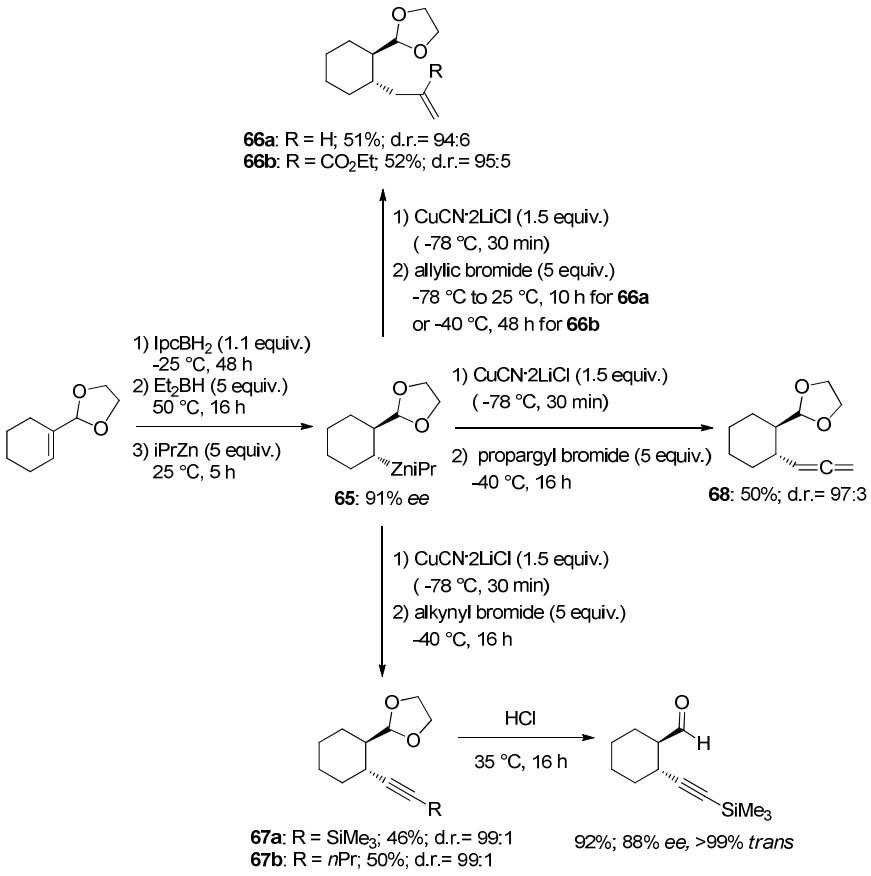
Thereby, the hydroboration proceeds with *anti*-Markovnikov- and *syn*-addition-selectivity and the B-Zn exchange with retention of stereoconfiguration. The configurational behaviour of these *trans*-configured organozinc reagents was examined using indanyl derivative ***trans*-62** (Scheme 21).[24]

[23] Boudier, A., Hupe, E. & Knochel, P. Highly diastereoselective synthesis of monocyclic and bicyclic secondary diorganozinc reagents with defined configuration. *Angew. Chem. Int. Ed. Engl.* **39**, 2294-2297 (2000).
[24] Boudier, A., Darcel, C., Flachsmann, F., Micouin, L., Oestreich, M. & Knochel, P. Stereoselective preparation and reactions of configurationally defined dialkylzinc compounds. *Chem. Eur. J.* **6**, 2748-2761 (2000).



Scheme 21: Deterioration of the diastereoselectivity in the quenching of ***trans*-62** with D_2O in the presence of $ZnBr_2$.

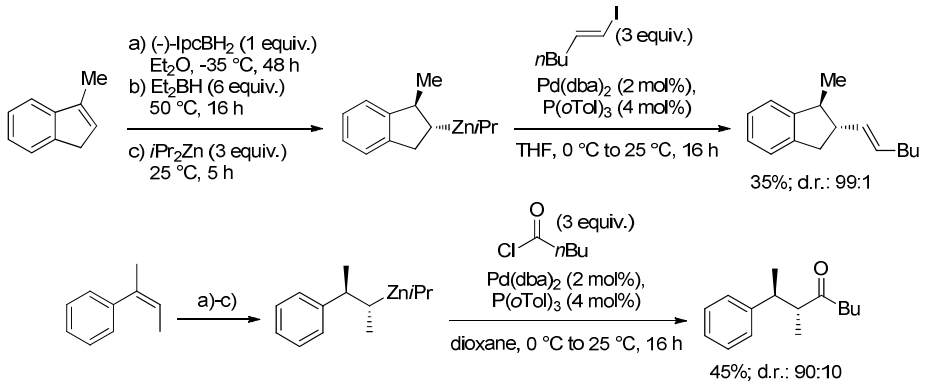
When ***trans*-62** was quenched at -78 °C with D_2O almost exclusively, as expected, the *trans*-deuterated product ***trans*-63** was formed. Prior addition of $ZnBr_2$ to ***trans*-62** at -78 °C for 20 min and subsequent quenching with D_2O, however, led to an erosion of the *trans*/*cis* ratio to 92:8. This method was extended to an enantioselective hydroboration/B-ligand exchange/B-Zn transmetalation sequence which allowed the preparation of the enantioenriched organozinc reagent **65** which was trapped with allylic, alkynyl and propargylic bromides to furnish the products **66-68** (Scheme 22).[25]



Scheme 22: Enantioselective conjugate functionalizations by an asymmetric hydroboration and B-Zn exchange sequence.

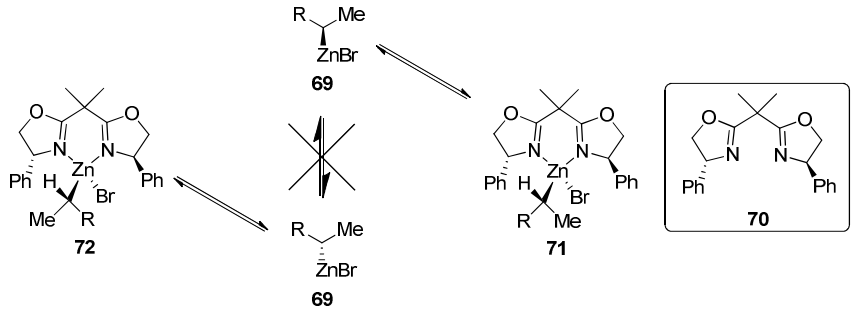
[25] Hupe, E. & Knochel, P. Formal enantioselective Michael addition with umpolung of reactivity. *Angew. Chem. Int. Ed. Engl.* **40**, 3022-3025 (2001).

Next to Cu-mediated trapping reactions with allyl bromides, also Pd-catalyzed acylations and cross-couplings with iodoalkenes has been described (Scheme 23).[26]



Scheme 23: Enantio- and diastereoselective preparation of cyclic and acyclic organozinc reagents and subsequent Pd-catalyzed cross-coupling and acylation.

The respective products were received with high diastereomeric ratios favouring the *trans*-configuration. Interestingly, a ^{1}H-NMR-investigation by *Rieke* and *Guijarro* on the configurational stability of secondary alkylzinc reagents, in which the racemic Zn-species **69** was complexed with a chiral bisoxazoline ligand (**70**) to give the distinguishable diastereomeric complexes **71** and **72**, showed that the C-Zn bond is configurationally extremely stable (Scheme 24).[27]



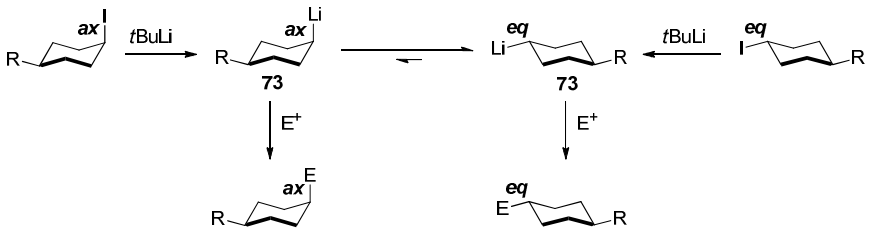
Scheme 24: High configurational stabilities for bisoxazoline-complexed diastereomeric secondary alkylzinc reagents **71** and **72**.

With no mentionable coalescence between these species being observed on an NMR-time scale, the authors calculated the lifetime of the inversion process to be 4130 h at 25 °C assuming a mononuclear transition state for inversion.

[26] Boudier, A. & Knochel, P. Palladium catalyzed stereoselective cross-couplings and acylations of chiral secondary diorganozincs. *Tetrahedron Lett.* **40**, 687-690 (1999).
[27] Guijarro, A. & Rieke, R. D. Study of the configuration stability of the carbon-zinc bond, direct measurement of enantiomeric ratios, and tentative assignment of the absolute configuration in secondary organozinc halides. *Angew. Chem. Int. Ed* **39**, 1475-1479 (2000).

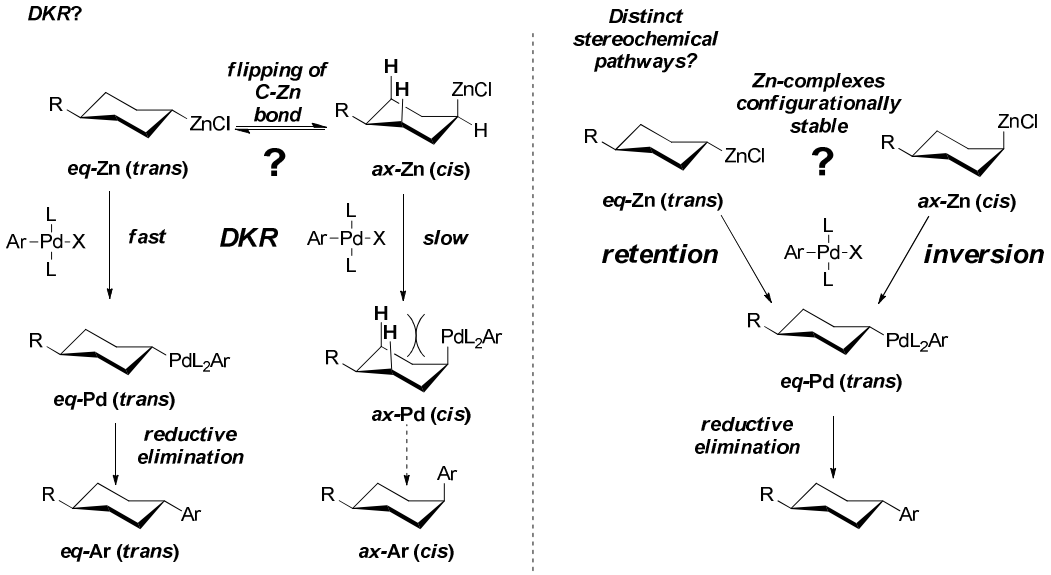
3. Objectives

One of the aims of this thesis was to develop a practical method for the preparation of stereodefined non-stabilized diastereomeric cyclohexyllithium reagents of type **73** so that their reactivities towards various electrophiles as well as their stereochemical behaviours could be investigated (Scheme 25).



Scheme 25: A stereoselective method for the generation of stereodefined cyclohexyllithium reagents – studies and explanations of their stereochemical behaviours.

Also, the stereochemical behaviour of diastereomeric cyclic zinc reagents should be examined in order to elucidate the true mechanism of their remotely controlled Pd-catalyzed diastereoselective *Negishi*-cross-coupling with aryl halides (Scheme 26).

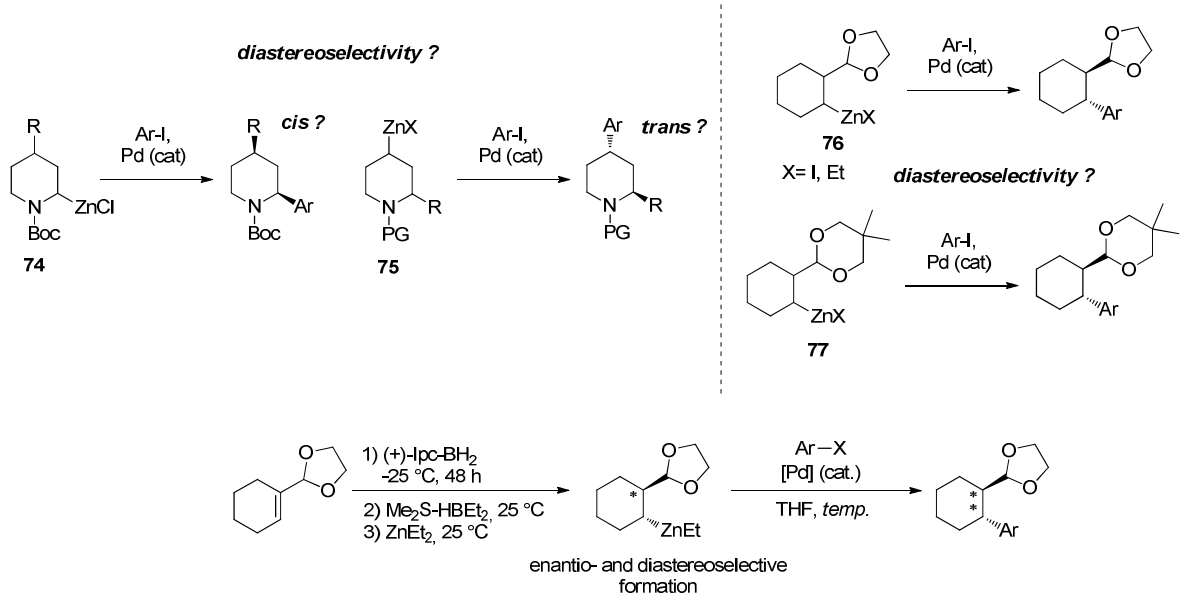


Scheme 26: Two plausible mechanistic scenarios for the stereoconvergent cross-coupling of substituted diastereomeric cyclohexylzinc reagents.

Although a dynamic kinetic resolution (*DKR*) mechanism had already been proposed (see Schemes 6 and 19), distinct kinetic preferences of the diastereomeric cyclohexylzinc complexes in the reaction with the arylpalladium complex cannot be ruled out (see Scheme 8)

especially since a high configurational stability of the C-Zn bond has been reported (see Scheme 24).[27]

Furthermore, the highly diastereoselective cross-coupling methodology should be extended to functionalized organozinc reagents, such as substituted piperidinylzinc reagents of types **74** and **75** and cyclohexylzinc reagents bearing functionalities, such as **76** and **77** (Scheme 27). Moreover, a method for a simultaneous enantio- and diastereoselective cross-coupling should be established.



Scheme 27: Diastereoselective cross-couplings of substituted piperidinylzinc and functionalized cycloalkylzinc reagents.

B. Results and Discussion

1. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted Cyclohexyllithium Derivatives

1.1. Introduction

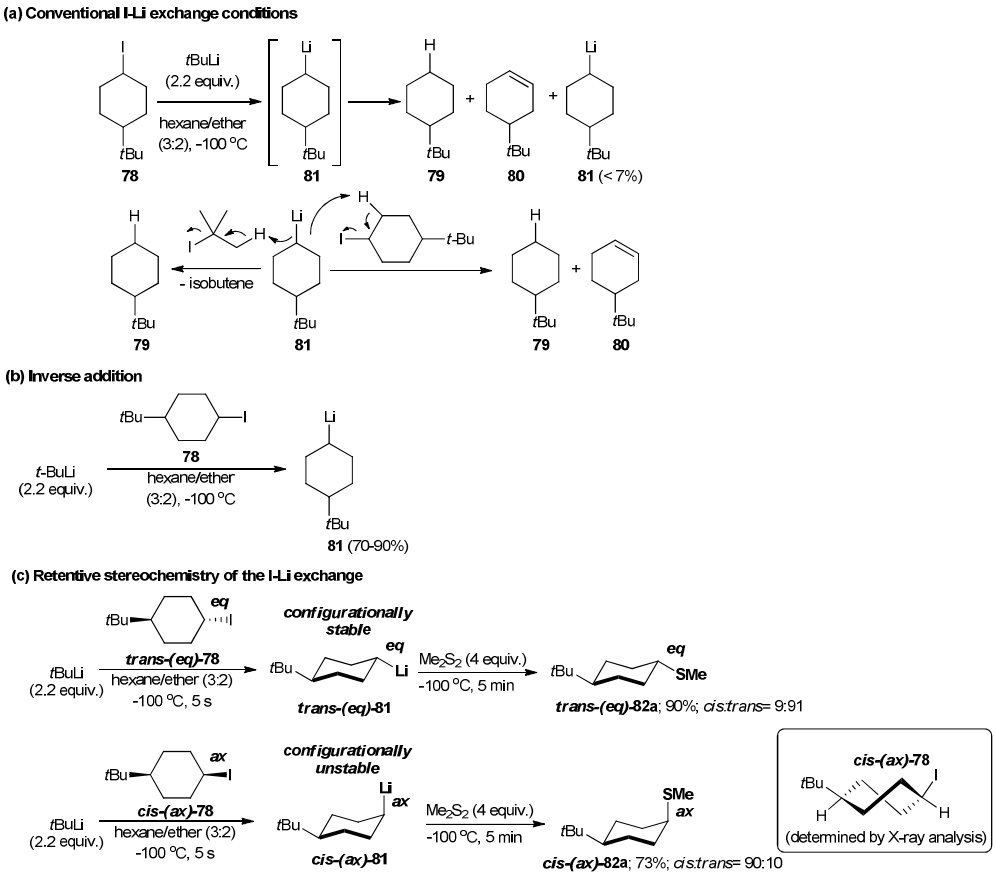
Although the stereoselective generation and stereochemistry of α-heteroatom-substituted alkyl-, benzylic and allylic organolithium reagents are well studied, the stereoselective preparation of non-stabilized secondary alkyllithiums remains a major synthetic challenge. In this work, a practical stereoretentive synthesis to unstabilized stereodefined cyclohexyllithium reagents from the readily available organic iodides via I-Li exchange is presented. Using this approach a detailed study on the configurational stabilities, stereochemical behaviour and reactivities of various axially and equatorially substituted cyclohexyllithium reagents was performed. Thus, the stereochemical paths (S_E2 vs. S_i2) of the quenching reactions were shown to depend on the respective cyclohexyllithium diastereomer and the electrophile. In all cases, the axial cyclohexyllithium was found to almost completely equilibrate into the configurationally stable, equatorial diastereomer. This inversion process was followed for differently substituted cyclohexyllithiums over time showing distinct behaviour. DFT-calculations demonstrated that the formation of oligomeric cyclohexyllithium structures is the key determinant for the observed stereochemical preference.

1.2. Results and Discussion

Initial experiments showed that the addition of *tert*-butyllithium (*t*BuLi) to a solution of 4-*tert*-butylcyclohexyl iodide (**78**) in hexane/ether (3:2)[28] at -100 °C gave mainly the protonation and elimination products **79** and **80** (Scheme 28a). This is due to a very similar reactivity of *t*BuLi and the newly formed secondary cyclohexyllithium **81**. Moreover, the mode of addition implies the presence of excess amounts of organic iodide **78** relative to

[28] a) Bailey, W. F. & Patricia, J. J. The mechanism of the lithium-halogen interchange reaction: a review of the literature. *J. Organomet. Chem.* **352**, 1-46 (1988); b) Bailey, W. F. & Punzalan, E. R. Convenient general method for the preparation of primary alkyllithiums by lithium-iodine exchange. *J. Org. Chem.* **55**, 5404-5406 (1990); c) Negishi, E.-I., Swanson, D. R. & Rousset, C. J. Clean and convenient procedure for converting primary alkyl iodides and α,ω-diiodoalkanes into the corresponding alkyllithium derivatives by treatment with *tert*-butyllithium. *J. Org. Chem.* **55**, 5406-5409 (1990); d) Bailey, W. F., Nurmi, T. T., Patricia, J. J. & Wang, W. Preparation and regiospecific cyclization of alkenyllithiums. *J. Am. Chem. Soc.* **109**, 2442-2448 (1987); e) Ashby, E. C. & Pham, T. N. Single electron transfer in metal-halogen exchange. The reaction of organolithium compounds with alkyl halides. *J. Org. Chem.* **52**, 1291-1300 (1987); f) Bailey, W. F., Brubaker, J. D. & Jordan, K. P. Effect of solvent and temperature on the lithium-iodine exchange of primary alkyl iodides: reaction of *t*-butyllithium with 1-iodooctane in heptane-ether mixtures. *J. Organomet. Chem.* **681**, 210-214 (2003).

organolithium species favouring elimination side-reactions. This results in a low yield of **81** (<7%; determined by quenching experiments, see below). However, inversion of the addition order[28] led to an efficient suppression of unwanted protonation and elimination pathways and the desired secondary cyclohexyllithium **81** was obtained in 70-90% yield. Using these optimized conditions, we were able to stereoselectively access various new non-stabilized secondary cyclohexyllithiums and, consequently, to probe their stereochemical behaviours.



Scheme 28: Optimization of the I-Li exchange conditions for 4-*t*-butyl-cyclohexyl iodide **78** and stereoselective generation of the corresponding lithium reagents ***trans-(eq)*-81** and ***cis-(ax)*-81**.

Thus, we have prepared the stereodefined *cis*- and *trans*-4-*tert*-butylcyclohexyl iodides ***cis-(ax)*-78**[29] (*cis/trans*= 98:2) and ***trans-(eq)*-78** (*cis/trans*= 10:90) from the respective cyclic alcohols[30] and subjected them to the I-Li exchange conditions described above. Addition of the stereodefined cyclohexyl iodide ***trans-(eq)*-78** (1.0 equiv., 1.0 M in 3:2 hexane/ether) to a solution of *t*BuLi (2.2 equiv., 0.2 M) cooled to -100 °C instantaneously produced the *trans*-

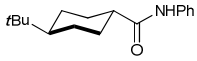
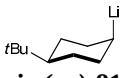
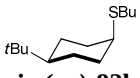
[29] CCDC/890872 (for ***β-(eq)*-94a**), CCDC/890873 (for ***cis-(ax)*-78**), CCDC/890874 (for ***neomen-(ax)*-91b**) and CCDC/890875 (for ***trans-(eq)*-82f**) contain supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

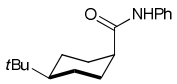
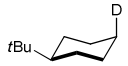
[30] Lange, G. L. & Gottardo, C. Facile conversion of primary and secondary alcohols to alkyl iodides. *Synth. Commun.* **20**, 1473–1479 (1990).

cyclohexyllithium reagent ***trans-(eq)*-81**. Quenching with Me_2S_2 (dimethyl disulfide; 4 equiv., -100 °C, 5 min) led to the expected *trans*-thioether ***trans-(eq)*-82a** with retention of configuration (*cis:trans*= 9:91) in a 90% yield (Scheme 28c). Notably, this *trans*-lithium reagent (***trans-(eq)*-81**) with the Li-atom occupying an equatorial position was stable at -100 °C for several hours (probed for a period of 7 h). Subjecting ***cis-(ax)*-78** to the same exchange reaction conditions produced the axially substituted *cis*-cyclohexyllithium ***cis-(ax)*-81** (-100 °C; 5 s). Quenching with Me_2S_2 (4 equiv., -100 °C, 5 min) mainly gave the corresponding *cis*-thioether ***cis-(ax)*-82a** (*cis:trans*= 90:10) in a 73% yield. The lithium species ***cis-(ax)*-81** bearing the Li-atom in an axial position displayed a much lower configurational stability and fully equilibrated into the stable all-equatorially substituted cyclohexyllithium ***trans-(eq)*-81** within 7 h at -100 °C (cis:trans <3:97; see also the detailed kinetic and theoretical studies on the configurational stability below). The lower stability of ***cis-(ax)*-81** compared to its diastereomer ***trans-(eq)*-81** is also likely to account for the slightly decreased yield.

Next, the reactivity of ***trans-(eq)*-81** and ***cis-(ax)*-81** towards a variety of electrophiles was examined (Table 1). While the reactions of ***trans-(eq)*-81** with a range of electrophiles proceeded with retention of configuration leading to the expected *trans*-substituted products in 85-92% yield and with excellent stereoselectivities (up to d.r. >99:1; entries 1-4; Table 1),

Table 1: Reactivities of ***trans*-** and ***cis*-81** with different electrophiles.

Entry	Li-Reagent	Electrophile	Product	d.r. (*cis*:*trans*)[a]	Yield [%][b]
1	 ***trans-(eq)*-81**	Bu_2S_2	 ***trans-(eq)*-82b**	<1:99	85
2	***trans-(eq)*-81**	Ph-NCO	 ***trans-(eq)*-82c**	<1:99	87
3	***trans-(eq)*-81**	F_3CCO_2D	 ***trans-(eq)*-82d**	4:96[c]	85[d]
4	***trans-(eq)*-81**	Me_3SnCl	 ***trans-(eq)*-82e**	<1:99	92
5	 ***cis-(ax)*-81**	Bu_2S_2	 ***cis-(ax)*-82b**	90:10	59

6	***cis-(ax)*-81**	Ph-NCO	 ***cis-(ax)*-82c**	90:10	60
7	***cis-(ax)*-81**	F_3CCO_2D	 ***cis-(ax)*-82d**	92:8[c]	75[d]
8	***cis-(ax)*-81**	Me_3SnCl	 ***trans-(eq)*-82e**	7:93	55
9	***cis-(ax)*-81**	Ph_3SnCl	 ***trans-(eq)*-82f**	8:92[e, f]	51

[a] Determined via capillary GC analysis and ^{1}H-NMR. [b] Isolated yields. [c] Determined via ^{2}H-NMR. [d] Determined via capillary GC analysis. [e] The relative configuration was determined by X-ray analysis.[29] [f] Determined via ^{119}Sn-NMR.

quenching of the configurationally labile ***cis-(ax)*-81** was not as predictable. Trapping of ***cis-(ax)*-81** with Bu_2S_2 (dibutyl disulfide), d-TFA and phenyl isocyanate (PhNCO) stereoselectively provided the expected *cis*-products (***cis-(ax)*-82b-d**; entries 5-7; Table 1). However, quenching of ***cis-(ax)*-81** with Me_3SnCl and Ph_3SnCl proceeded with inversion resulting mainly in the *trans*-substituted stannanes (***trans-(eq)*-82e-f**; entries 8 and 9; Table 1).[31] Due to the greater lability of ***cis-(ax)*-81** lower yields (51-75%) are generally obtained than in the reactions of ***trans-(eq)*-81**. The configurational instability of ***cis-(ax)*-81** also accounts for the lower observed stereoselectivities in the retentive quenching reactions (entries 5-7; Table 1).

Intrigued by these results, we became interested in the scope of substrates suitable for the I-Li exchange reaction. Therefore, we chose a variety of differently substituted cyclohexyl iodides and subjected them to the I-Li exchange conditions. First, the reactions of equatorially substituted cyclohexyl iodides, which lead to the configurationally more stable organolithium reagents, were examined (Table 2).

[31] a) Hoppe, D., Carstens, A. & Krämer, T. Generation of a configurationally stable chiral benzyllithium derivative, and the capricious stereochemistry of its electrophilic substitution. *Angew. Chem. Int. Ed. Engl.* **29**, 1424-1425 (1990); b) Hammerschmidt, F., Hanninger, A & Völlenkle, H. Proof of inversion of configuration on stannylation of a configurationally stable, tertiary benzyllithium compound from a single-crystal X-ray structure analysis. *Chem. Eur. J.* **3**, 1728-1732 (1997).

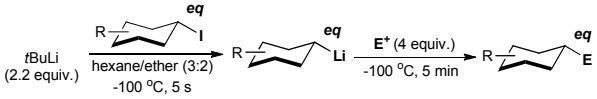
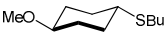
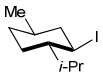
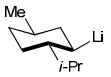
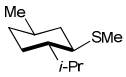
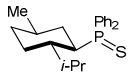
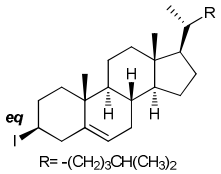
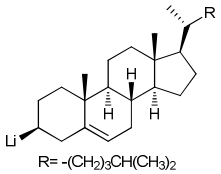
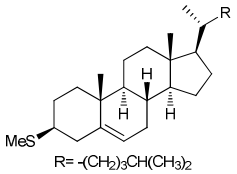
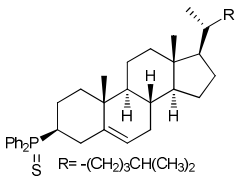
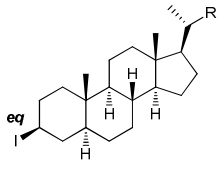
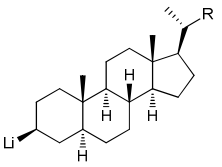
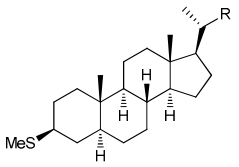


Table 2: Scope study of the I-Li exchange using equatorially substituted cyclohexyl iodides and quenching of the ensuing Li-species with electrophiles.

Entry	Cyclohexyl Iodide	Cyclohexyllithium	E^+	Product	d.r. *ax:eq*[a]	Yield [%][b]
1	 ***trans-(eq)*-83a**	 ***trans-(eq)*-84a**	Bu_2S_2	 ***trans-(eq)*-85a**	<1:99	91
2	 ***trans-(eq)*-83b**	 ***trans-(eq)*-84b**	Bu_2S_2	 ***trans-(eq)*-85b**	<1:99	83
3	 ***trans-(eq)*-83c**	 ***trans-(eq)*-84c**	Bu_2S_2	 ***trans-(eq)*-85c**	1:99	90
4	***trans-(eq)*-83c**	***trans-(eq)*-84c**	Ph_2PCl, S_8	 ***trans-(eq)*-85d**	2:98	69
5	***trans-(eq)*-83c**	***trans-(eq)*-84c**	$EtSO_2Cl$	 ***trans-(eq)*-85e**	1:99	61
6	 ***cis-(eq)*-86a**	 ***cis-(eq)*-87a**	Bu_2S_2	 ***cis-(eq)*-88a**	1:99	81
7	 ***cis-(eq)*-86b**	 ***cis-(eq)*-87b**	Bu_2S_2	 ***cis-(eq)*-88b**	2:98	63
8	 ***men-(eq)*-89**	 ***men-(eq)*-90**	Me_2S_2	 ***men-(eq)*-91a**	13:87	54
9	***men-(eq)*-89**	***men-(eq)*-90**	Ph_2PCl, S_8	 ***men-(eq)*-91b**	10:90[d]	59
10	 ***β-(eq)*-92**	 ***β-(eq)*-93**	Me_2S_2	 ***β-(eq)*-94a**	1:99[c]	71
11	***β-(eq)*-92**	***β-(eq)*-93**	Ph_2PCl, S_8	 ***β-(eq)*-94b**	6:94[e]	80

12	 (d.r.: 85:15) R= -$(CH_2)_3CH(CH_3)_2$ ***β-(eq)*-95**	 R= -$(CH_2)_3CH(CH_3)_2$ ***β-(eq)*-96**	Me_2S_2	 R= -$(CH_2)_3CH(CH_3)_2$ ***β-(eq)*-97**	2:98	74

[a] Determined via capillary GC analysis and ^{1}H-NMR. [b] Isolated yields. [c] The relative configuration was determined by X-ray analysis.[29] [d] Determined via ^{31}P-NMR. [e] Determined via ^{1}H-NMR.

Thus, the 4-methyl-substituted cyclohexyl iodide (***trans-(eq)*-83a**) was stereoselectively converted to the organolithium reagent ***trans-(eq)*-84a** which upon trapping with Bu_2S_2 exclusively provided the *trans*-configured thioether ***trans-(eq)*-85a** in 91% yield (entry 1; Table 2). Replacing the methyl group with coordinating (MeO; ***trans-(eq)*-84b**) and non-coordinating (TIPSO; TIPS= *i*-Pr_3Si; ***trans-(eq)*-84c**) oxygen functionalities led, after quenching, to the expected *trans*-substituted products with equally high yields and diastereoselectivities (83-90%; d.r.: >99:1; entries 2-3; Table 2). Trapping of the functionalised organolithium reagent ***trans-(eq)*-84c** with Ph_2PCl and subsequent protection with S_8 gave the *trans*-substituted thiophosphane ***trans-(eq)*-85d** in 69% overall yield with a d.r. of 98:2 (entry 4; Table 2). The reaction of ***trans-(eq)*-84c** with $EtSO_2Cl$ exclusively led to the all-equatorially substituted cyclohexyl chloride ***trans-(eq)*-85e** (entry 5; Table 2). The *cis*-1,3-disubstituted cyclohexyl iodides ***cis-(eq)*-86a-b** smoothly underwent the I-Li exchange reaction. The resulting equatorially substituted Li-reagents ***cis-(eq)*-87a-b** were trapped with Bu_2S_2 leading to the *cis*-configured products ***cis-(eq)*-88a-b** with 63-81% yield and high diastereoselectivities (entries 6 and 7; Table 2). Subjection of menthyl iodide (***men-(eq)*-89**) with a diastereomeric purity of 75:25 (menthyl(***eq***)/neomenthyl(***ax***)) to the I-Li exchange reaction resulted in the formation of mainly menthyllithium (***men-(eq)*-90**) whose immediate quenching with Me_2S_2 or Ph_2PCl gave the menthyl derivatives ***men-(eq)*-91a-b** with improved diastereoselectivities relative to the starting material reaching from 87:13 to 90:10 (entries 8-9; Table 2). The comparatively low yields (54-59%) can be attributed to the increased basicity of ***men-(eq)*-90** which competes more readily with *t*BuLi for deprotonation of the *tert*-butyl iodide (*t*BuI) side-product (compare Scheme 28) and to the presence of 25% neomenthyl iodide (***neomen-(ax)*-89**) in the starting material which leads to an unstable axial organolithium (***neomen-(ax)*-90**; see Table 3). I-Li exchange on cholesteryl iodide ***β-(eq)*-92** led to the configurationally stable Li-reagent ***β-(eq)*-93** which underwent quenching with Me_2S_2 and Ph_2PCl with retention of stereoconfiguration furnishing the products ***β-(eq)*-94a**[29] and ***β-(eq)*-94b** with 71-80% yield and high stereoselectivities (d.r. 94:6 to 99:1; entries 10-

11, Table 2). Subjection of cholestanyl iodide ***β-(eq)*-95** with a diastereomeric purity of 85:15 (β/α) to the I-Li exchange and subsequent trapping of the resulting lithium compound ***β-(eq)*-96** with Me_2S_2 gave the thioether ***β-(eq)*-97** in 74% yield with a significantly increased diastereomeric ratio of 98:2 in favour of the β-isomer (entry 12, Table 2). Next, we examined the substrate scope of the corresponding axially substituted cyclohexyllithium reagents (***cis-(ax)*-84a-c**, ***trans-(ax)*-87**, ***neomen-(ax)*-90**) by subjecting the respective stereochemically pure cyclohexyl iodides (***cis-(ax)*-83a-c**, ***trans-(ax)*-86**, ***neomen-(ax)*-89**) to the I-Li exchange conditions (Table 3).

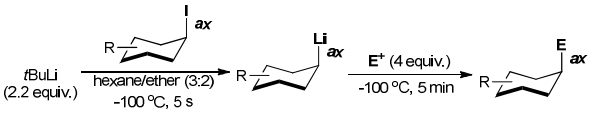
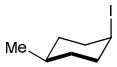
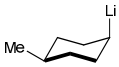
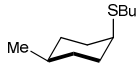
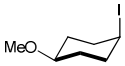
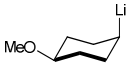
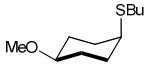
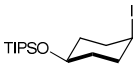
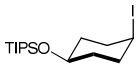
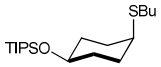
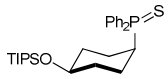
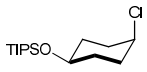
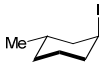
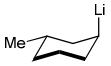
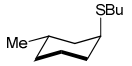
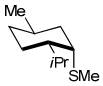
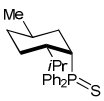
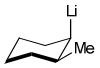
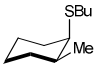
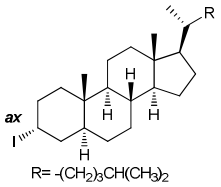
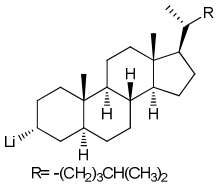
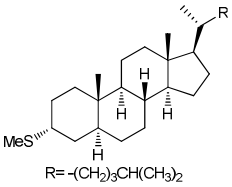


Table 3: Scope study of the I-Li exchange using axially substituted cyclohexyl iodides and quenching of the ensuing Li-species with electrophiles.

Entry	Cyclohexyl Iodide	Cyclohexyllithium	E^+	Product	d.r. *ax:eq*[a]	Yield [%][b]
1	 ***cis-(ax)*-83a**	 ***cis-(ax)*-84a**	Bu_2S_2	 ***cis-(ax)*-85a**	91:9	74
2	 ***cis-(ax)*-83b**	 ***cis-(ax)*-84b**	Bu_2S_2	 **85b**	52:48	67
3	 ***cis-(ax)*-83c**	 ***cis-(ax)*-84c**	Bu_2S_2	 ***cis-(ax)*-85c**	96:4	79
4	***cis-(ax)*-83c**	***cis-(ax)*-84c**	Ph_2PCl, S_8	 ***cis-(ax)*-85d**	92:8	51
5	***cis-(ax)*-83c**	***cis-(ax)*-84c**	$EtSO_2Cl$	 ***cis-(ax)*-85e**	94:6	56
6	 ***trans-(ax)*-86**	 ***trans-(ax)*-87**	Bu_2S_2	 ***trans-(ax)*-88**	89:11	56
7	 ***neomen-(ax)*-89**	 ***neomen-(ax)*-90**	Me_2S_2	 ***neomen-(ax)*-91a**	93:7	23
8	***neomen-(ax)*-89**	***neomen-(ax)*-90**	Ph_2PCl, S_8	 ***neomen-(ax)*-91b**	91:9[c,d]	28

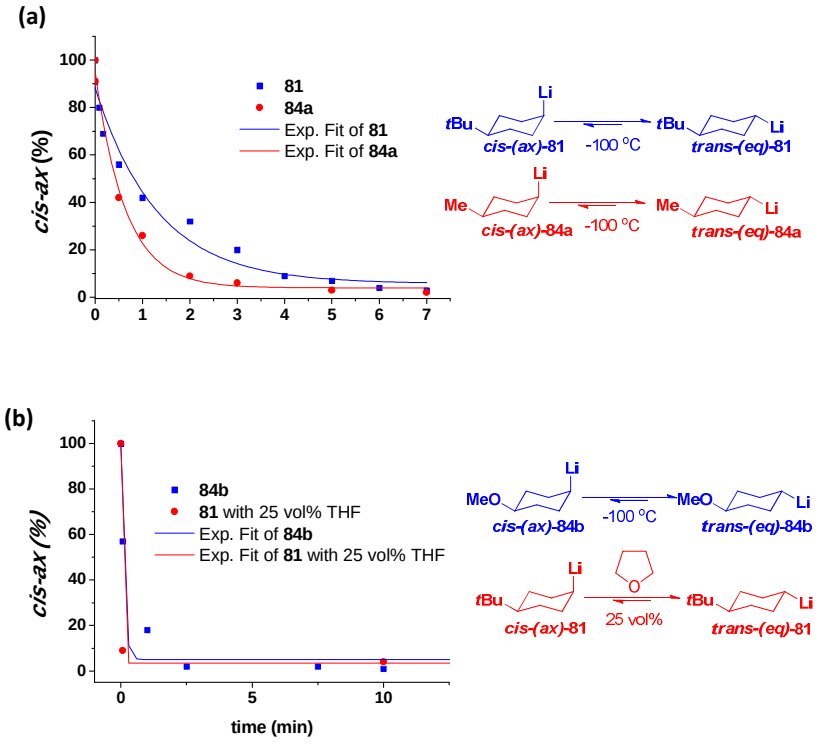
9	 ***cis-(ax)*-98**	 ***cis-(ax)*-99**	Bu_2S_2	 ***cis-(ax)*-100**	88:12	34
10	 ***α-(ax)*-95**	 ***α-(ax)*-96**	Me_2S_2	 ***α-(ax)*-97**	77:23	18

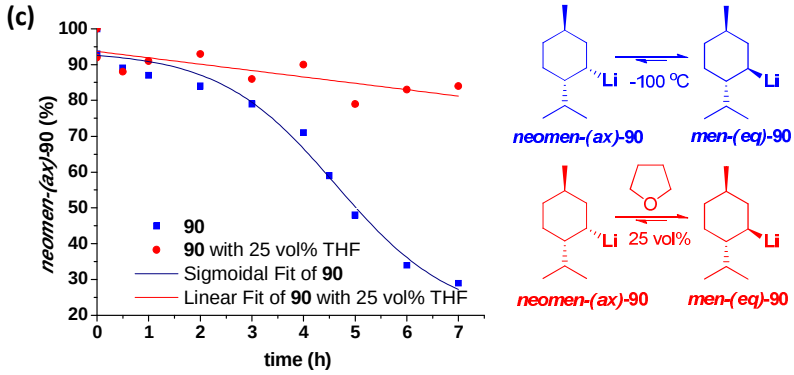
[a] Determined via capillary GC analysis and ^{1}H-NMR. [b] Isolated yields. [c] Determined via ^{31}P-NMR. [d] The relative configuration was determined by X-ray analysis.[29]

Thus, the 4-methyl-substituted *cis*-configured cyclohexyllithium ***cis-(ax)*-84a** generated from the corresponding axial iodide ***cis-(ax)*-83a** gave the expected product ***cis-(ax)*-85a** after immediate trapping (5 s) with Bu_2S_2 with predominant retention of configuration (d.r.: 91:9, 74%; entry 1 of Table 3). Remarkably, when the I-Li exchange was performed on the 4-methoxy-substituted cyclohexyl iodide ***cis-(ax)*-83b**, immediate quenching with Bu_2S_2 led to a 52:48 *cis*:*trans*-mixture of the thioether **85b** (entry 2, Table 3). We reasoned that this decay in stereoselectivity could be attributed to the coordinative properties of the 4-MeO-group which may intramolecularly break the unstable C-Li bond and facilitate its isomerization to the configurationally more stable equatorially substituted organolithium ***trans-(eq)*-84b**. Indeed, complete isomerisation from ***cis-(ax)*-84b** to ***trans-(eq)*-84b** takes place within only 2.5 min at -100 °C in a hexane:ether 3:2-mixture (*cis*:*trans* 2:98; see also the detailed kinetic studies on the configurational stability below; Scheme 29b), whereas the corresponding 4-*tert*-butyl-substituted axial cyclohexyllithium ***cis-(ax)*-81** requires 7 h under the same conditions to isomerise to the stable equatorial cyclohexyllithium compound ***trans-(eq)*-81** (see also Scheme 29a). Interestingly, accelerated isomerization was not observed with an OTIPS-substituent and the desired *cis*-configured products ***cis-(ax)*-85c-e** were obtained upon quenching in 51-79% yield with stereoselectivities up to 96:4 (entries 3-5, Table 3). The bulky silyl group prevents the neighbouring oxygen atom from coordinating to the Li^+-ion. I-Li exchange on the 3-methyl-substituted *trans*-configured cyclohexyl iodide ***trans-(ax)*-86** led to formation of configurationally unstable ***trans-(ax)*-87** which upon immediate quenching with Bu_2S_2 gave the expected product ***trans-(ax)*-88** with 56% yield and a slightly decreased d.r. of 89:11 (entry 6, Table 3). Immediate trapping of neomenthyllithium (***neomen-(ax)*-90**), generated from neomenthyl iodide (***neomen-(ax)*-89**), with Me_2S_2 and Ph_2PCl furnished the axially substituted products with good stereoselectivities (d.r. 91:9 to 93:7), however, in low

yields (23-28%; entries 7-8, Table 3). The decreased yields are due to a highly reactive neomenthyllithium species (***neomen-(ax)*-90**) whose C-Li bond is weakened by the neighbouring isopropyl-group. Thus, the higher reactivity of this C-Li bond makes it a better competitor for *t*BuLi in the deprotonation of *t*BuI explaining the lower yields (compare Scheme 28a). Similar results were obtained in the quenching of the *cis*-2-methyl-substituted cyclohexyllithium ***cis-(ax)*-99** which was generated from iodide ***cis-(ax)*-98**. Trapping of ***cis-(ax)*-99** with Bu_2S_2 led to the product ***cis-(ax)*-100** with a good diastereomeric ratio of 88:12 in 34% yield (entry 9, Table 3) underlining the higher reactivity and greater instability of 2-substituted cyclohexyllithium species with an axial C-Li bond. We have also prepared the more complex epicholestanyl iodide ***α-(ax)*-95** and subjected it to an I-Li exchange. The resulting organolithium species ***α-(ax)*-96** was immediately quenched with Me_2S_2. The axially substituted product ***α-(ax)*-97** was predominantly obtained (*α*/*β*: 77:23) albeit in a low yield (18%; entry 10, Table 3). Presumably, the large cholestanyl moiety in ***α-(ax)*-96** hampers the formation of stabilizing oligomeric organolithium-clusters (see also DFT-analysis below).

Next, we followed the kinetics of the invertive equilibration processes under standard conditions at -100 °C for the 4-substituted cyclohexyllithium reagents ***cis-(ax)*-81**, ***cis-(ax)*-84a** and ***cis-(ax)*-84b** (Scheme 29a-b). The ratio of axial to equatorial Li-species, determined via retentive quenching with Me_2S_2 or Bu_2S_2, was recorded during a time course of 7 h.





Scheme 29: Kinetic investigation on the equilibration of the configurationally unstable axially substituted cyclohexyllithium reagents into their stable equatorially substituted diastereomers.

Plotting of the percentage of the respective axial 4-substituted cyclohexyllithium species versus time resulted in near-exponential curves for ***cis-(ax)*-81** and ***cis-(ax)*-84a** showing that invertive equilibration proceeds with first-order rate kinetics. Interestingly, the inversion process was faster for ***cis-(ax)*-84a** bearing the less bulky methyl group in position 4. Thus, after 2 h, an *ax*/*eq*-ratio of 9:91 was reached for **84a**, whereas the 4-*tert*-butyl-substituted cyclohexyllithium **81** had only equilibrated to a ratio of 32:68 in the same time period. After 7 h, ***cis-(ax)*-81** and ***cis-(ax)*-84a** had almost completely been converted to the diastereomeric configurationally stable Li-species ***trans-(eq)*-81** (*ax*/*eq*: 3:97) and ***trans-(eq)*-84a** (*ax*/*eq*: 2:98). Equilibration towards the more stable equatorially substituted cyclohexyllithium ***trans-(eq)*-84b** proceeded much faster for ***cis-(ax)*-84b** due to facilitated C-Li bond breakage via intramolecular coordination of the Li-atom to the methoxy-moiety. Here, after already 5 s, an *ax*/*eq*-ratio of 52:48 is reached. After 2.5 min ***cis-(ax)*-84b** has almost completely equilibrated to the diastereomeric isomer ***trans-(eq)*-84b** (*ax*/*eq*: 2:98). Thus, we wondered whether addition of THF, which is known to be a strongly coordinating solvent for organolithium species,[32] to ***cis-(ax)*-81** would similarly accelerate its equilibration to the stable ***trans-(eq)*-81**. Indeed, when 25 vol% THF were added to ***cis-(ax)*-81** at -100 °C immediate quenching

[32] a) Gronert, S. & Streitwieser, Jr., A. Carbon acidity. 71. The indicator scale of lithium ion pairs in tetrahydrofuran. *J. Am. Chem. Soc.* **108**, 7016-7022 (1986); b) Carbone, G., O'Brien, P. & Hilmersson, G. Asymmetric deprotonation using *s*BuLi or *i*PrLi and chiral diamines in THF: the diamine matters. *J. Am. Chem. Soc.* **132**, 15445-15450 (2010); c) Reich, H. J. & Borst, J. P. Direct nuclear magnetic resonance spectroscopic determination of organolithium ion pair structures in THF/HMPA solution. *J. Am. Chem. Soc.* **113**, 1835-1837 (1991); d) Bauer, W., Winchester, W. R. & von Ragué Schleyer, P. Monomeric organolithium compounds in tetrahydrofuran: *tert*-butyllithium, *sec*-butyllithium, "supermesityllithium", mesityllithium, and phenyllithium. Carbon-lithium coupling constants and the nature of carbon-lithium bonding. *Organometallics* **6**, 2371-2379 (1987); e) Kwon, O., Sevin, F. & McKee, M. L. Density functional calculations of methyllithium, *t*-butyllithium, and phenyllithium oligomers: effect of hyperconjugation on conformation. *J. Phys. Chem. A* **105**, 913-922 (2001).

with Me_2S_2 already displayed an *ax*/*eq*-ratio of 9:91. Quenching after 10 min gave the product ***trans-(eq)*-82a** in 63% isolated yield with a d.r. of 4:96.

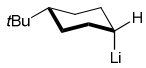
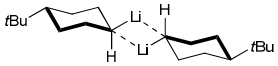
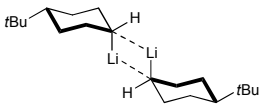
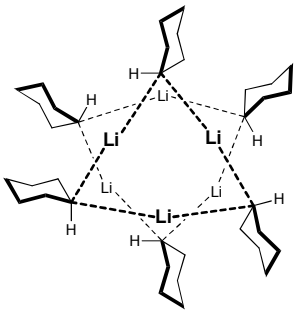
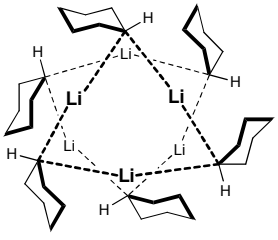
When we turned our attention to the kinetics of C-Li bond inversion with neomenthyllithium ***neomen-(ax)*-90** bearing a large isopropyl group in the neighbouring position, we were surprised to find a completely different behaviour. Its equilibration followed a sigmoidal curve. Thus, inversion was very slow during the first 4 h reaching only an *ax*/*eq*-ratio of 71:29. After 4 h, the curve's slope got steeper showing an accelerated inversion resulting in an *ax*/*eq*-ratio of 29:71 after 7 h. This hints towards an auto-mediated process in which menthyllithium ***men-(eq)*-90** promotes its own formation. With enough menthyllithium ***men-(eq)*-90** (ca. 30%) formed, inversion accelerates. However, the overall inversion proceeds much slower than for the 4-substituted cyclohexyllithiums. Almost complete inversion from ***neomen-(ax)*-90** to ***men-(eq)*-90** could be achieved when the reaction mixture was warmed, directly after I-Li exchange on ***neomen-(ax)*-89**, from -100 °C to -60 °C within 50 min. Quenching of the lithium reagent with Me_2S_2 gave ***men-(eq)*-91a** with a high stereoselectivity (*ax/eq*= 2:98) and 32% yield. Notably, addition of 25 vol% of THF did not speed up the equilibration from ***neomen-(ax)*-90** to ***men-(eq)*-90** at -100 °C. Instead, the *ax*/*eq*-ratio changed much more slowly over time. In this case, the kinetic behaviour was best described by a straight line. After 7 h, the *ax*/*eq*-ratio had only dropped to 84:16.

In order to explore the preference of lithium for the equatorial over the axial positions in cyclohexane ring systems, theoretical studies have been performed for 4-*tert*-butylcyclohexyllithium **81** in its equatorial (***trans-(eq)*-81**) and axial (***cis-(ax)*-81**) configurations. Following earlier theoretical work on organolithium species[32,33] geometry optimizations have been performed at the B3LYP/6-31+G(d) level of theory. Thermal corrections to free energies at 298.15 K have been calculated at the same level using the rigid rotor/harmonic oscillator model. Single point energies have then been added at MP2(FC)/6-311+G(2d,p) level and combined with thermal corrections obtained at B3LYP/6-31+G(d) level in order to calculate free energies at 298.15 K. Interestingly, comparison of the gas phase stabilities of monomeric ***trans-(eq)*-81** and ***cis-(ax)*-81** indicated a small thermodynamic preference for the axially substituted ***cis-(ax)*-81** (Table 4) by 3.8 kJ/mol. This energy difference remains essentially unchanged at even higher levels of theory such as G3+(MP2)B3. This, however, is in clear contrast to the trapping experiments performed at

[33] a) Hæffner, F. & Brinck, T. How does methyllithium invert? A density functional study. *Organometallics* **20**, 5134-5138 (2001); b) Ando, K. Theoretical study on the lithium-halogen exchange reaction of 1,1-dihaloalkenes with methyllithium and the nucleophilic substitution reaction of the resulting α-halo alkenyllithiums. *J. Org. Chem.* **71**, 1837-1850 (2006).

-100 °C in Et_2O/hydrocarbon solvents demonstrating a large or exclusive preference for equatorial isomers. Since the experimentally observed strong stereochemical preference for the equatorially substituted ***trans-(eq)*-81** may be due to aggregates formed at low temperatures in weakly coordinating solvents, calculations have been additionally performed on the respective cyclohexyllithium aggregates. Comparison of the gas phase stabilities of the dimeric lithium species ***trans-(eq)*-101** and ***cis-(ax)*-101** shows only a small preference of 4.72 kJ/mol for the equatorial isomer (Table 4). The hexameric structures found for *n*BuLi[34] (from hexane) and cyclohexyllithium[35] (from benzene) indicate that higher aggregates can easily be formed in less polar solvents. The equatorial/axial preference was therefore also explored for the hexameric form of cyclohexyllithium.

Table 4: Relative gas phase stabilities of monomeric, dimeric and hexameric cyclohexyllithiums.

Entry	**Structures[a], $\Delta G_{298/ax\text{-}eq}$ [kJ/mol][b]**	
	 ***trans-(eq)*-81**	 ***cis-(ax)*-81**
1	-3.8	
	 ***trans-(eq)*-101**	 ***cis-(ax)*-101**
2	+4.7	
	 ***trans-(eq)*-102**	 ***cis-(ax)*-102**
3	+71.3	

[a] Geometries have been optimized at the B3LYP/6-31+G(d) level in all cases. [b] Energies were determined at the MP2(FC)/6-311+G(2d,p) level.

[34] Kottke, T & Stalke, D. Structures of classical reagents in chemical synthesis: $(n\text{BuLi})_6$, $(t\text{BuLi})_4$, and the metastable $(t\text{BuLi}\bullet Et_2O)_2$. *Angew. Chem. Int. Ed Engl.* **32**, 580-582 (1993).

[35] Zerger, R., Rhine, W. & Stucky, G. Stereochemistry of polynuclear compounds of the main group elements. The bonding and the effect of metal-hydrogen-carbon-interactions in the molecular structure of cyclohexyllithium, a hexameric organolithium compound. *J. Am. Chem. Soc.* **96**, 6048-6055 (1974).

Despite the fact that this system now lacks the *t*butyl anchor at position 4 of the cyclohexane ring, the results are nevertheless expected to be also relevant for the substituted system. The results obtained at B3LYP or MP2 level of theory are quite clear about the strong preference for the all-equatorial isomer ***trans-(eq)*-102** over the all axial isomer ***cis-(ax)*-102**, in agreement with the conformation found in the hexameric X-ray crystal structure.[35] The large energy difference of 71.3 kJ/mol in favour of ***trans-(eq)*-102** implies a preference of 11.9 kJ/mol for the equatorial orientation in each of the six monomers. Compared to the equatorial/axial energy differences found for the respective *t*butyl cyclohexyllithium monomers (***trans-(eq)*-81** and ***cis-(ax)*-81**) and dimers (***trans-(eq)*-101** and ***cis-(ax)*-101**), this implies that the state of aggregation is the key determinant for the stereochemical preferences in substituted cyclohexyllithiums.

In summary, we have described a practical preparation of stereodefined cyclohexyllithium reagents from the corresponding organic iodides. This stereoretentive method allowed a detailed study of the configurational stabilities, stereochemical behaviours and reactivities of a wide range of axially and equatorially substituted cyclohexyllithium reagents. Thus, it was possible to stereoselectively synthesize various *cis*- and *trans*-cyclohexane derivatives by quenching with several classes of electrophiles. We have also found a clear tendency of equilibration towards the equatorially substituted lithium compounds. This thermodynamic phenomenon was explained by the formation of hexameric organolithium species which display a large difference in energy for the all-equatorial and all-axial species as proven by DFT-calculations. Polar solvents, such as THF, speed up the equilibration process for axial 4-substituted cyclohexyllithium reagents, while they display a stabilization effect on 2-substituted neomenthyllithium ***neomen-(ax)*-90**. An invertive reactivity pathway was found for the reaction of configurationally labile axially substituted cyclohexyllithium ***cis-(ax)*-81** with organotin halides.

2. Novel Insights into the Stereochemical Behaviour of Diastereomeric Cyclohexylzinc Reagents – Stereoconvergence through Distinct Stereochemical Pathways

2.1. Introduction

Whereas the reactivities and configurational stabilities of diverse stereodefined alkyllithium[36] and -magnesium species[37] have been subject to extensive studies, the stereochemical behaviour of organozinc species has only been sporadically investigated. The C-Zn bond plays an exceptional role in organometallic chemistry, as it has a significantly more covalent character than C-Li and C-Mg bonds which results in a broad compatibility towards sensitive functional groups.[38] Still, the reactivity of organozinc reagents is considerably increased compared to the corresponding organoboron reagents making them highly useful reagents for organic synthesis.[38] A stereoselective preparation of secondary alkylzinc reagents, however, proved difficult and the B-Zn exchange reaction so far represents the only general method for generating stereodefined C-Zn bonds.[39] Only a few more examples for the stereoselective

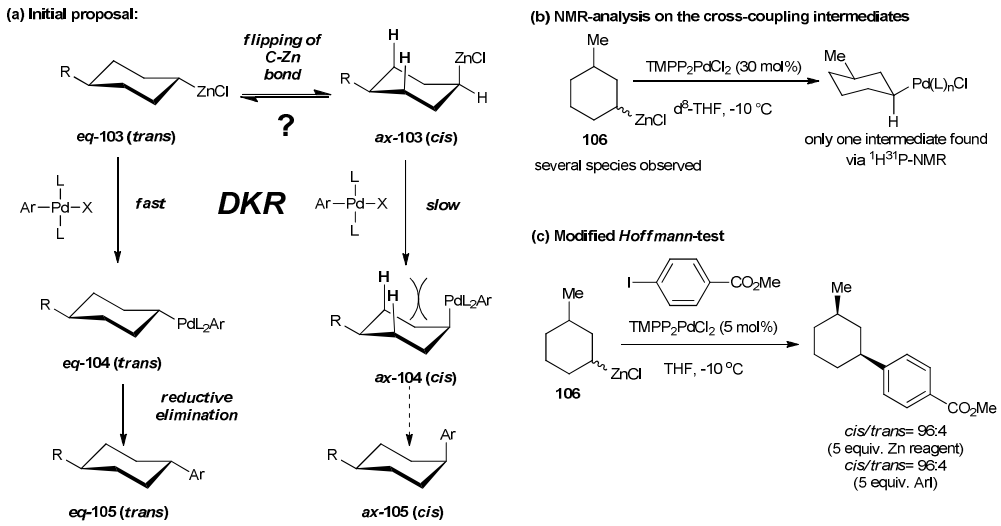
[36] a) Clayden, J. *Organolithiums: Selectivity for Synthesis* (Elsevier, Philadelphia, 2002); b) Gawley, R. E. & Siegel, J. S. *Topics in Stereochemistry - Stereochemical Aspects of Organolithium Compounds* Vol. 26 (VHCA, Zürich, Wiley-VCH, Weinheim, 2010); c) Lee, W. K., Park, Y. S. & Beak, P. Dynamic thermodynamic resolution: Advantage by separation of equilibration and resolution. *Acc. Chem. Res.*, 224-234 (2009); d) Basu, A. & Thayumanavan, S. Configurational stability and transfer of stereochemical information in the reactions of enantioenriched organolithium reagents. *Angew. Chem. Int. Ed.* **41**, 716-738 (2002); e) Hoppe, D. & Hense, T. Enantioselective synthesis with lithium/(-)-sparteine carbanion pairs. *Angew. Chem. Int. Ed. Engl.* **36**, 2282-2316 (1997); f) Hoppe, D. α-Metallated O-2-alkenyl carbamates: synthetic equivalents of chiral homoenolates and materials for asymmetric homoaldol reaction. *Synthesis*, 43-55 (2009); g) Lee, W. K., Park, Y. S. & Beak, P. Dynamic thermodynamic resolution: Advantage by separation of equilibration and resolution. *Acc. Chem. Res.*, 224-234 (2009).

[37] a) Hoffmann, R. W. The quest for chiral Grignard reagents. *Chem. Soc. Rev.* **32**, 225-230 (2003); b) Jensen, F. R. & Nakamaye, K. L. Preparation of geometrically isomeric Grignard reagents and the stereochemical courses of their reactions. *J. Am. Chem. Soc.* **88**, 3437-3438 (1966); c) Whitesides, G. M. & Roberts, J. D. Nuclear magnetic resonance spectroscopy. The configurational stability of primary Grignard reagents. *J. Am. Chem. Soc.* **87**, 4878-4888 (1965); d) Beckmann, J., Dakternieks, D., Dräger, M. & Duthie, A. New insights into the classic chiral Grignard reagent (1*R*,2*S*,5*R*)-menthylmagnesium chloride. *Angew. Chem. Int. Ed. Engl.* **45**, 6509-6512 (2006).

[38] Knochel, P. *Handbook of functionalized organometallics: applications in synthesis.* Vol. 1 (Wiley-VCH, Weinheim, 2005).

[39] a) Micouin, L., Oestreich, M. & Knochel, P. Stereoselective preparation and reactions of cycloalkylzinc compounds. *Angew. Chem. Int. Ed.* **36**, 245-246 (1997); b) Boudier, A., Darcel, C., Flachsmann, F., Micouin, L. Oestreich, M. & Knochel, P. Stereoselective preparation and reactions of configurationally defined dialkylzinc compounds. *Chem. Eur. J.* **6**, 2748-2761 (2000); c) Boudier, A., Hupe, E. & Knochel, P. Highly diastereoselective synthesis of monocyclic and bicyclic diorganozinc reagents with defined configuration. *Angew. Chem. Int. Ed.* **39**, 2294-2297 (2000); d) Hupe, E. & Knochel, P. Formal enantioselective Michael addition with umpolung of reactivity. *Angew. Chem. Int. Ed.* **40**, 3022-3025 (2001); e) Hupe, E., Knochel, P. & Szabó, K. J. Mechanism of the stereoselective alkyl group exchange between alkylboranes and alkylzinc compounds. Quest for novel types of boron-metal exchange reactions. *Organometallics* **21**, 2203-2207 (2002); f) Hupe, E., Calaza, M. I. & Knochel, P. Synthesis and reaction of secondary and primary diorganozinc reagents using a boron-zinc exchange reaction. A useful method for the stereo- and regioselective formation of new carbon-carbon bonds. *J. Org. Chem.* **680**, 136-142 (2003).

preparations of secondary alkylzinc reagents have been reported. Thus, Zn-insertion using the highly active *Rieke*-Zn into diastereomerically pure *endo*-2-acetamido-7-iodobicyclo[2.2.1]heptane was stated to proceed with retention of configuration. Stereoconvergence leading to the *exo*-configured organozinc species was observed with *exo*- and *endo*-7-iodonorcaranes using the same conditions.[40] However, the respective organozinc compounds have not been directly analyzed and all conclusions on their stereoconfiguration have been deduced from quenching experiments with I_2 and Me_3SnCl. Recently, a stereoconvergent remotely stereocontrolled cross-coupling between substituted cyclohexylzinc reagents and (hetero)aryl halides[41] and alkynyl bromides was disclosed.[42] In a preliminary mechanistic proposal, a relatively fast equilibration between the diastereomeric cyclohexylzinc reagents was assumed and the observed high diastereoselectivities in the coupling reactions were ascribed to a dynamic kinetic resolution process[43] in which the equatorially substituted cyclohexylzinc reagent ***eq*-103** would react faster than the axially substituted conformer ***ax*-103** leading selectively to the Pd-intermediate ***eq*-104** and after reductive elimination to the all equatorially substituted arylated product ***eq*-105** (Scheme 30).[41,42]



[40] Duddu, R., Eckhardt, M., Furlong, M., Knoess, H. P., Berger, S. & Knochel, P. Preparation and reactivity of chiral β–amido-alkylzinc iodides and related configurationally stable zinc organometallics. *Tetrahedron* **50**, 2415-2432 (1994).

[41] Thaler, T., Haag, B., Gavryushin, A., Schober, K., Hartmann, E., Gschwind, R., Zipse, H., Mayer, P. & Knochel, P. Highly diastereoselective Csp^3-Csp^2 Negishi cross-coupling with 1,2-, 1,3- and 1,4-substituted cycloalkylzinc compounds. *Nature Chem.* **2**, 125-130 (2010).

[42] Thaler, T., Guo, L.-N., Mayer, P. & Knochel, P. Highly diastereoselective C(sp^3)-C(sp) cross-coupling reactions between 1,3- and 1,4-substituted cyclohexylzinc reagents and bromoalkynes through remote stereocontrol. *Angew. Chem. Int. Ed.* **50**, 2174-2177 (2011).

[43] a) Pellissier, H. Recent developments in dynamic kinetic resolution. *Tetrahedron* **67**, 3769-3802 (2011); b) Pellissier, H. Recent developments in dynamic kinetic resolution. *Tetrahedron* **64**, 1563-1601 (2008); c) Pellissier, H. Dynamic kinetic resolution. *Tetrahedron* **59**, 8291-8327 (2003).

Scheme 30: Initial mechanistic proposal showing a dynamic kinetic resolution (DKR) process for the stereoconvergence observed in the Pd-catalyzed cross-couplings of substituted cyclohexylzinc reagents with aryl halides (a). A relatively fast equilibrium between the diastereomeric cyclohexylzinc reagents was postulated due to the results of a modified *Hoffmann*-test (b). NMR studies indicated that only one cyclohexylpalladium intermediate was formed with the palladium occupying the equatorial position, whereas signals for several organozinc species were found (c). The DKR proposal is based on these experimental observations.

This model suited best, at that time, the experimental results and theoretical calculations. Thus, a modified *Hoffmann*-test[44] on the configurational stability of 3-methylcyclohexylzinc chloride (**106**) using a five-fold excess of aryl iodide (electrophile) or zinc reagent (nucleophile) was performed. Since in both cases, the same d.r. had been achieved, it was concluded that the C-Zn bond was configurationally unstable and a DKR process would be the reason for the observed stereoconvergence. In combination with the fact that only one cyclohexylpalladium intermediate was observed using $^{1}H^{31}P$-NMR, in which the Pd-moiety occupied the equatorial position, and with the DFT-calculations that showed significant energetic differences only for the cyclohexylpalladium intermediates, however, not for the corresponding cyclohexylzinc compounds, this seemed a judicious approach.

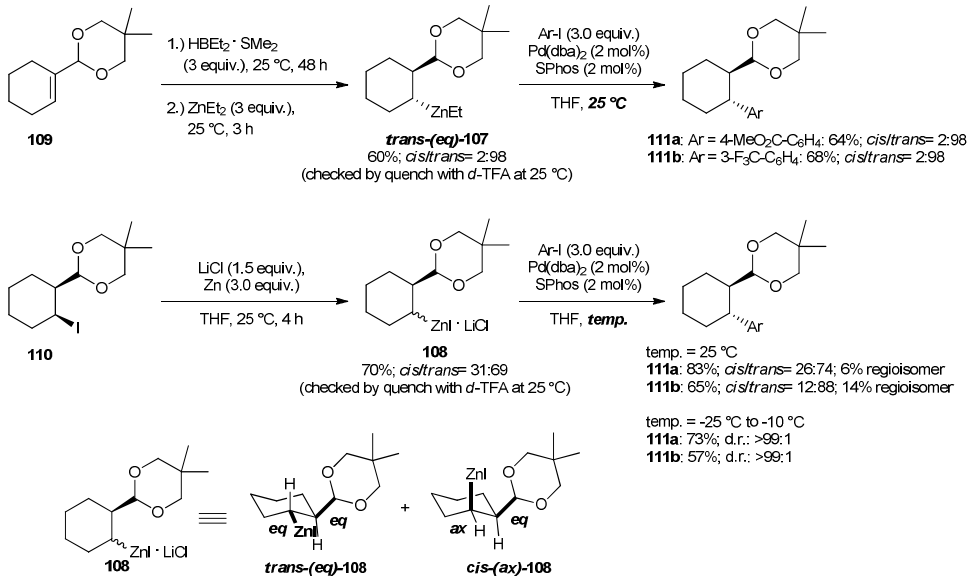
The results of the modified *Hoffmann*-test, still, are ambiguous due to two reasons: 1) It was performed on a Pd-catalyzed reaction. Thus, reaction with excess or substoichiometric amounts of nucleophile would always have to pass through the bottleneck of a catalytic amount of Pd-intermediate. 2) Diastereomeric organozinc compounds were examined. For two diastereomeric reagents the stereochemical course (retention vs. inversion) of substitution with electrophiles does not have to be identical, since, in contrast to the isoenergetic reaction pathways of enantiomers, the pathways for diastereomers can differ in energy. Although not yet experimentally proven, *Basu* and *Thayumanavan* had anticipated such a scenario in a seminal review on the configurational stability of organolithium compounds.[36d] Thus, with our preliminary mechanistic investigations, we could not exclude the possibility of distinct stereochemical pathways for the two diastereomeric cyclohexylzinc derivatives in the transmetalation with Ar-PdL_nX. Importantly, the configurational stability of secondary organozinc reagents has been contradictorily discussed in the literature: *Guijarro* and *Rieke* have published a comprehensive NMR-study on the configurational stability of (*R*)-and (*S*)-

[44] a) Hoffmann, R. W., Julius, M., Chemla, F., Ruhland, T. & Frenzen, D. Configurational stability of chiral organolithium compounds on the time scale of their addition to aldehydes *Tetrahedron* **50**, 6049-6060 (1994); b) Hirsch, R. & Hoffmann, R. W. A test on the configurational stability of chiral organolithium compounds based on kinetic resolution; scope and limitations. *Chem. Ber.* **125**, 975-982 (1992); c) Klute, W., Dress, R. & Hoffmann, R. W. Enantioselective transformations of configurationally labile α-phenylselenoalkyllithium compounds. *J. Chem. Soc. Perkin Trans.* ***2***, 1409-1411 (1993).

sec-butylzinc bromide using a chiral bisoxazoline-ligand.[45] The resulting diastereomeric complexes displayed distinct proton signals for the methine group and could thus be probed for equilibration. An extremely slow inversion process was observed ($t_{1/2}$= 4.0 months!). Early experiments from our laboratories with stereodefined secondary alkylzinc reagents, however, suggested that the presence of salts considerably decreased the stability of the C-Zn bond by deteriorating the observed diastereoselectivities in quenching reactions with D_2O.[39b] A DKR process and thus configurational lability were also hypothesized by *Hayashi* and *Kumada* for the enantioselective coupling of (1-phenylethyl)zinc halides with vinyl bromide using a chiral Pd-ferrocene catalyst.[46]

2.2. Results and Discussion

Intrigued by these contradictory reports, we decided to get more deeply involved in the study of the stereochemical behaviour of diastereomeric cyclohexylzinc systems in order to disclose the true reasons for the observed stereoconvergence in their diastereoselective *Negishi*-couplings.



Scheme 31: *Negishi*-cross-coupling on the structurally identical substituted cyclohexylzinc reagents ***trans-(eq)*-107** and **108** displaying different stereochemical purities.

[45] Guijarro, A. & Rieke, R. D. Study of the configuration stability of the carbon-zinc bond, direct measurements of enantiomeric ratios, and tentative assignment of the absolute configuration in secondary organozinc halides *Angew. Chem. Int. Ed.* **39**, 1475-1479 (2000).

[46] Hayashi, T., Hagihara, T., Katsuro, Y. & Kumada, M. Asymmetric cross-coupling of organozinc reagents with alkenyl bromides catalyzed by a chiral ferrocenylphosphine-palladium complex. *Bull. Chem. Soc. Jpn.* **56**, 363-364 (1983).

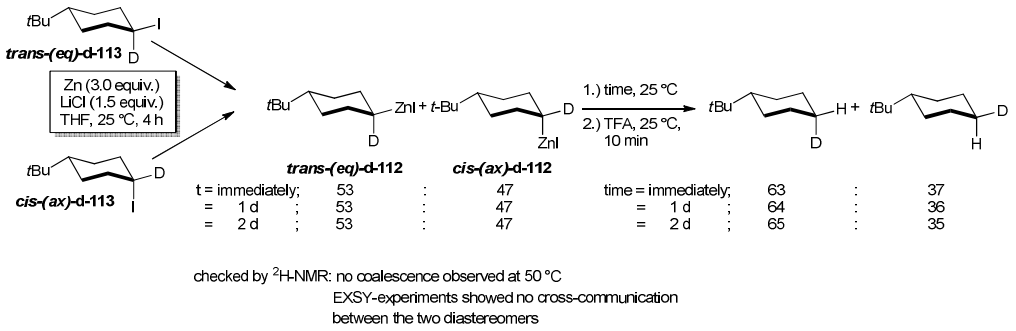
In preliminary experiments, we prepared the 2-substituted cyclohexylzinc reagents ***trans-(eq)*-107** and **108** which are structurally identical but differ in stereochemical purity and subjected them to our *Negishi*-cross-coupling conditions (Scheme 31). While ***trans-(eq)*-107** (*trans:cis*= 98:2) was stereoselectively prepared using hydroboration on **109** followed by a stereoretentive B-Zn exchange,[39] **108** was obtained as a mixture of diastereomers (*trans:cis*= 69:31) from LiCl-promoted Zn-insertion into the corresponding organic iodide **110**.[47,48] The stereochemical purity of these compounds was checked by deuterolysis with d-TFA (10 equiv.) at RT. All equatorially substituted ***trans-(eq)*-107** was then subjected to *Negishi*-cross-couplings using $Pd(dba)_2$ (2 mol%; dba: dibenzylideneacetone) and SPhos (2 mol%; dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine)[49] as catalyst system with several aryl iodides at RT. The respective arylated products **111a-b** were obtained after 12-24 h in 90-93% yield (64-68% overall yield). Their diastereomeric purity (*trans:cis*= 98:2) completely reflected the stereochemical content of the starting organozinc ***trans-(eq)*-107**. Thus, the cross-couplings had proceeded with complete retention of stereoconfiguration. When the diastereomerically undefined **108** underwent the identical cross-coupling conditions with the same aryl iodides, **111a-b** were obtained with 65-83% yield and diastereomeric ratios reaching from *trans:cis* 74:26 to 88:12. The diastereomeric purity had increased compared to the starting zinc reagent **108**. In addition, however, the formation of regioisomers was observed (6-14%). Strikingly, when the cross-couplings were performed at lower temperatures (-25 °C to -10 °C), solely the all equatorially substituted, thermodynamically favourable *trans*-configured products were obtained (57-83% yield; *trans:cis* >99:1). The formation of regioisomers was thereby not observed. These results made us question our previous hypothesis of a DKR-driven stereoconvergence for two main reasons: 1) The configurationally defined, equatorially substituted ***trans-(eq)*-107** reacted smoothly to give the products **111a-b** with the same diastereomeric ratio, which does not corroborate the presumption of a fast equilibration between two thermodynamically almost equally favoured cyclohexylzinc diastereomers. 2) The observation of regioisomers in the cross-coupling reactions of stereochemically undefined **108** suggests that the axially substituted ***cis-(ax)*-108** diastereomer may undergo distinct reaction pathways from ***trans-(eq)*-108**.

[47] Krasovskiy, A., Malakhov, V., Gavryushin, A. & Knochel, P. Efficient synthesis of functionalized organozinc compounds by the direct insertion of zinc into organic iodides and bromides. *Angew. Chem. Int. Ed.* **45**, 6040-6044 (2006).

[48] Cohen, T., Gibney, H., Ivanov, R., Yeh, E. A.-H., Marek, I. & Curran, D. P. Intramolecular carbozincation of unactivated alkenes occurs through a zinc radical transfer mechanism. *J. Am. Chem. Soc.* **129**, 15405-15409 (2007).

[49] Barder, T. E., Walker, S. D., Martinelli, J. R. & Buchwald, S. L. Catalysts for Suzuki-Miyaura coupling processes: scope and studies of the effect of ligand structure *J. Am. Chem. Soc.* **127**, 4685-4696 (2005).

In order to determine whether C-Zn bonds can invert on a relatively fast time scale (hours or minutes) and whether a fast equilibration was therefore possible, we decided to probe the configurational stability of ***trans-(eq)*-d-112** and ***cis-(ax)*-d-112** (Scheme 32).



Scheme 32: Test on the configurational stability of the C-Zn bond in substituted diastereomeric ***cis-(ax)*-d-113** and ***trans-(eq)*-d-113**.

The remotely substituted cyclohexylzinc reagent **d-112** (***trans-(eq)*-d-112** & ***cis-(ax)*-d-112**) which bears a *tert*-butyl-substituent in position 4 and a deuterium on carbon 1 geminal to the zinc enabled us to directly observe the stereochemical purity of the organozinc via ^{2}H-NMR. The bulky *tert*-butyl-group also functions as an anchor for the cyclohexyl ring ensuring that the diastereomeric zinc reagents differ only in the configuration of the C-Zn bond (axial (*cis*) vs. equatorial (*trans*)). Zn-insertion into the stereodefined 4-*tert*-butylcyclohexyl iodides ***cis*-d-113** and ***trans*-d-113** resulted both in a *cis*:*trans*-mixture of **d-112** (53:47). No change in the ratio was observed after 2 d at RT. EXSY-experiments showed no cross-signal for neither the deuterium in ^{2}H- nor the deuterated carbon in ^{13}C-NMR analysis over a period of 12 h. When the EXSY experiments were applied to **112**, bearing a proton instead of the deuterium, cross-signals could be found for neither the methine proton nor carbon. A significant coalescence-shift was not observed in the ^{2}H-NMR analysis of **d-112** even upon heating to 50 °C. Subjection of **d-112** to quenching with TFA immediately and even after standing for 2 d at room temperature further confirmed the observed configurational stability of the cyclohexylzinc reagents.

It was now clear to us that due to the high configurational stability of the C-Zn bond a DKR mechanism which implies an equilibration between the diastereomeric zinc reagents and thus flipping of the C-Zn bond cannot be the cause of the observed stereoconvergence in the *Negishi* cross-coupling (Scheme 30). The mechanistic possibilities were now limited to either an equilibration on the stage of the Pd-intermediate (***eq*-104**; Scheme 30), a Pd-salt induced equilibration or different stereochemical pathways for the diastereomeric cyclohexylzinc

reagents in which the equatorial C-Zn bond would react with retention and the axial C-Zn bond with inversion of stereoconfiguration in the transmetalation step selectively forming ***eq*-104**. Thus, aware of the pivotal influence of temperature on the diastereoselectivity in the *Negishi*-cross-coupling (Scheme 31), we decided to probe the stereochemistry of several diastereomeric cyclohexylzinc reagents in the deuterolysis with d-TFA and MeOD at different temperatures (Table 5).

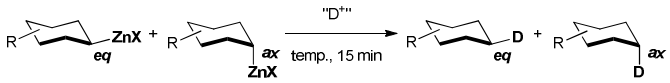
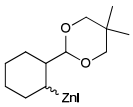
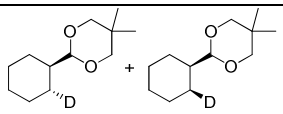
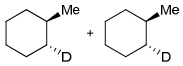
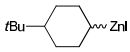
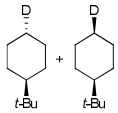
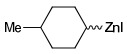
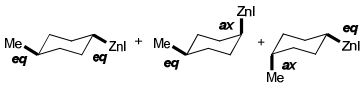
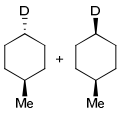
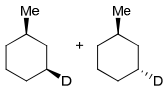
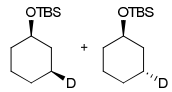
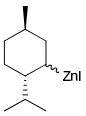
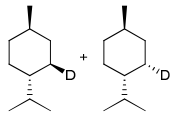
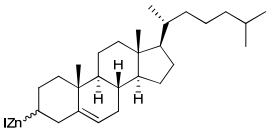
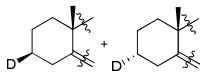
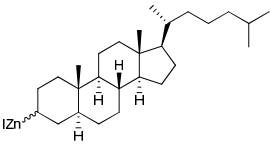
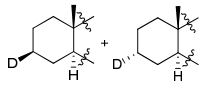
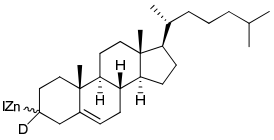
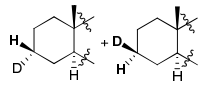
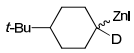
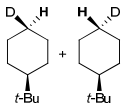


Table 5: Deuterolysis of diastereomeric cyclohexylzinc reagents.

Entry	Cyclohexylzinc Reagent	D^+/H^+-Source	Reaction Temp. [°C]	Products	d.r. (*eq:ax*)[a]
1	 **108**	d-TFA	25	 ***trans-(eq)*-114** + ***cis-(ax)*-114**	69:31
2		d-TFA	-78		99:1
3		MeOD	25		99:1
4	 **115**	d-TFA	25	 ***trans-(eq)*-116** + ***cis-(ax)*-116**	48:52
5		d-TFA	-78		96:4
6		MeOD	25		87:13
7		MeOD	0		97:3
8	 **112**	d-TFA	25	 ***trans-(eq)*-117** + ***cis-(ax)*-117**	67:33
9		d-TFA	-78		>99:1
10		MeOD	25		>99:1
11	 **118** ≡  ***trans-(eq)*-118** + ***cis-(ax1)*-118** + ***cis-(ax2)*-118**	d-TFA	25	 ***trans-(eq)*-119** + ***cis-(ax)*-119**	66:34
12		d-TFA	-78		76:24
13		MeOD	25		76:24
14		MeOD	0		90:10
15	 **120**	d-TFA	25	 ***cis-(eq)*-121** + ***trans-(ax)*-121**	65:35
16		d-TFA	-78		80:20
17		MeOD	25		76:24
18		MeOD	0		90:10

19	 **122**	d-TFA	25	 ***cis-(eq)*-123** + ***trans-(ax)*-123**	58:42
20		d-TFA	-78		79:21
21		MeOD	25		66:44
22		MeOD	0		84:16
23	 **124**	d-TFA	25	 ***men-(eq)*-125** + ***neomen-(ax)*-125**	65:35
24		d-TFA	-78		>99:1
25		MeOD	25		>99:1
26	 **126**	d-TFA	25	 ***β-(eq)*-127** + ***α-(ax)*-127**	82:18
27		d-TFA	-78		>99:1
28		MeOD	25		>99:1
29	 **128**	d-TFA	25	 ***β-(eq)*-129** + ***α-(ax)*-129**	79:21
30		d-TFA	-78		99:1
31		MeOD	25		90:10
32		MeOD	0		>99:1
33	 **d-126**	TFA	25	 ***α-(ax)*-127** + ***β-(eq)*-127**	88:12
34	 **d-112**	TFA	25	 ***cis-(ax)*-117** + ***trans-(eq)*-117**	64:36
35		TFA	-78		63:37
36		MeOH	25		**87:13**
37		MeOH	0		**91:9**

[a] Determined via ^{2}H-NMR.

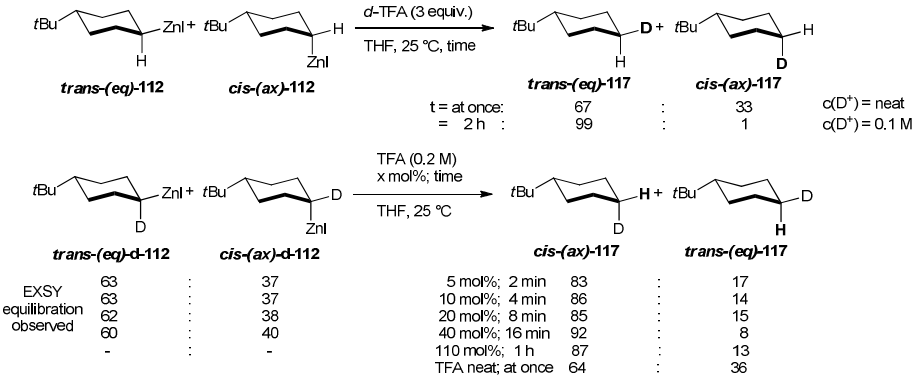
Thus, quenching of **108** with d-TFA, which had resulted in a *cis:trans*-ratio of 31:69 at RT, led almost exclusively to the *trans*-configured deuterated product ***trans-(eq)*-114** (*cis(ax):trans(eq)*= 1:99) when performed at -78 °C (entries 1-2). Remarkably, replacing the strong acid d-TFA with the weak D^{+}-source MeOD furnished ***trans-(eq)*-114** (*cis(ax):trans(eq)*= 1:99) upon quenching at RT (entry 3). A similar behaviour was found for **115** bearing a less sterically demanding methyl-group in position 2 (entries 4-7). Interestingly, a *cis(ax)/trans(eq)*-ratio of deuterated product **116** of 13:87 was obtained when quenched with MeOD at RT (entry 6). This d.r. could be further improved to 3:97 when the reaction temperature was decreased to 0 °C (entry 7). For **112** bearing the *tert*-butyl anchor in position 4, the identical clear trend was observed: While quenching with d-TFA revealed the true

diastereomeric ratio of **112** (*cis:trans*= 33:67), exclusively ***trans-(eq)*-117** was obtained when the reaction was performed at -78 °C (entries 8-9). Quenching with MeOD at RT gave ***trans-(eq)*-117** with a diastereomeric purity of >99:1 (entry 10). Using **118** in which the *tert*-butyl anchor is replaced by a smaller methyl-group which allows the presence of an additional conformer for the axial *cis*-configured diastereomer ***cis-(ax2)*-118** in which the methyl-group occupies an axial position while the C-Zn bond is oriented equatorially. Thus, the trend towards the all equatorially substituted, deuterated *trans*-product ***trans-(eq)*-119** upon quenching at low temperature and with the weaker acid MeOD is less pronounced (entries 11-14). Upon quenching with MeOD at 0 °C a *cis:trans*-ratio of only 10:90 was achieved (entry 14). Almost identical ratios were obtained for the deuterolysis products ***cis-(eq)*-121** and ***trans-(ax)*-121** of the 3-methyl-substituted cyclohexylzinc reagent **120** (entries 15-18). The 3-OTBS-substituted **122**, in accordance with the lower a-value of oxygen-groups on cyclohexyl rings,[50] displayed a smaller bias towards equatorial deuteration, as reflected by the ratio of ***cis-(eq)*-123** and ***trans-(ax)*-123** (entries 19-22). With MeOD-quenching at 0 °C, however, a *trans(ax):cis(eq)*-ratio of 84:16 was achieved (entry 19). The rigid menthyl- (**124**), cholesteryl- (**126**) and cholestanylzinc (**128**) reagents showed a very strong tendency towards equatorial deuteration with both d-TFA and MeOD (entries 23-32). Thus, for menthylzinc reagent **124**, which gave a 65:35 mixture of ***men-(eq)*-125** to ***neomen-(ax)*-125** upon trapping with d-TFA at RT, only the menthyl-diastereomer ***men-(eq)*-125** was obtained, when the temperature was decreased to -78 °C (entry 24). Also, quenching with MeOD at RT resulted only in the formation of ***men-(eq)*-125** (entry 25). For rigid cholesteryl- (**126**) and cholestanylzinc iodide (**128**) quenching with d-TFA at RT resulted already in α*(ax):* β*(eq)*-ratios of 18:82 and 21:79 (entries 26 and 29). Quenching with d-TFA at -78 °C and MeOD resulted in a strong preference for the equatorially deuterated products ***β-(eq)*-127** and ***β-(eq)*-129** (entries 27-28, 30-32). In order to test whether these trends hold also true for protolysis, we performed analogous quenching reactions with the deuterated cyclohexylzinc iodides **d-126** and **d-112** using TFA and MeOH as proton sources (entries 33-37).[51] Quenching **d-126** with TFA at room temperature resulted already in a d.r. of 88:12 for the equatorially protonated product, thus corroborating the tendencies which were observed with the deuterolysis of **126** before (compare entries 26 and 33). The results for protolysis of **d-112** were more remarkable: While trapping of **d-112** with TFA at -78 °C and at RT both resulted in the same diastereomeric ratio (*cis:trans*= 36:64; 37:63; entries 34-35), quenching with

[50] Eliel, E. L. *Stereochemistry of carbon compounds* (McGraw-Hill, New York, 1962).
[51] Giagou, T. & Meyer, M. P. Kinetic isotope effects in asymmetric reactions. *Chem. Eur. J.* **16**, 10616-10628 (2010).

MeOH, however, resulted in preferential equatorial protonation with *cis:trans*-ratios of 13:87 at RT and 9:91 at 0 °C (entries 36-37). This unequivocally proves the tendency of the axial C-Zn bond in the *cis*-configured diastereomer ***cis-(ax)*-d-112** to undergo invertive quenching.

We also observed a dependence of the diastereoselectivity in the quenching reactions on the mode of addition (Scheme 33). While direct quenching of **112** with d-TFA at RT resulted in a *cis:trans*-ratio of 33:67, slow addition of d-TFA over 2 h gave almost exclusively ***trans-(eq)*-117**. (A test experiment showed that this result was a function of the time used for addition, not of the lower concentration of d-TFA.) The same trend was observed in the protolysis of **d-112** with TFA.



Scheme 33: Comparison of direct and slow addition of d-TFA addition to **112**.

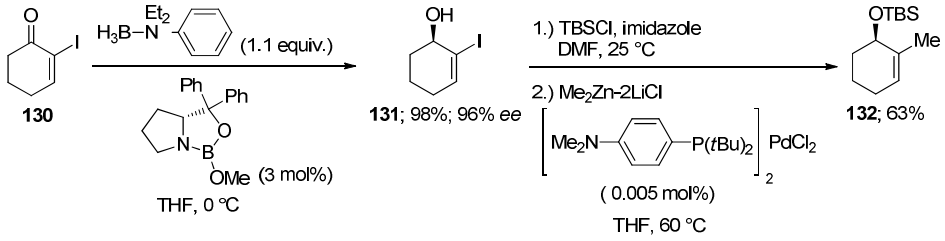
Thereby, addition of TFA over 2 h led preferentially to ***cis-(ax)*-d-112** (*cis:trans*= 89:11). The distinct chemical shifts of the deuterium atoms on **d-112** (prepared without LiCl) and on the protonated products allowed us to follow the protolysis reaction of **d-112** via ^{2}H-NMR. Thus, TFA was added slowly via syringe pump and the d.r. of **d-112** and the protonation product **117** was checked after several periods of time. Remarkably, the starting d.r. of **d-112** (*cis(ax-Zn):trans(eq-Zn)*= 37:63) remained constant during addition of TFA. More strikingly even, the d.r. of the protonated compound did not alter considerably. Thus, when 5 mol% TFA were added after 2 min, already a *cis(ax-H):trans(ax-H)*-ratio of 83:17 was observed for **117**. This ratio remained more or less the same after the addition of 20 mol% TFA after 20 min (85:15) and after 1 h, when quenching of **d-112** was finished after 1 h upon a total 110 mol% TFA (87:13). Accompanying ^{2}H-EXSY-NMR experiments showed no observable cross-peak, thus excluding an equilibration of the C-Zn bond on NMR timescale. These results along with the fact that only one Pd-intermediate could be observed in the cross-coupling show that the equatorial C-Zn bond must react with retention and the axial C-Zn bond with inversion of the stereoconfiguration in the transmetalation step to $ArPdL_nX$ thus leading to stereoconvergence

in the reaction. Therefore, we replace the DKR scenario with a mechanistic view in which the two diastereomeric cyclohexylzinc reagents react via distinct stereochemical (retentive vs. invertive) pathways.

3. Diastereo- and Enantioselective Cross-Coupling with Functionalized Cyclohexylzinc Reagents

3.1. Synthesis of Chiral Protected Cyclohexyl Derivatives for the Enantio- and Diastereoselective Synthesis of 1-, 2-, 3-trisubstituted Cyclohexanes

The diastereoselective cross-coupling of substituted cyclohexylzinc derivatives should be applied to chiral functionalized building blocks. For this purpose, the chiral **131** was synthesized from 2-iodocyclohex-2-enone[52] (**130**) *via* CBS-catalysis[53] using diethylaniline borane in 98% yield and 96% *ee*. Subsequent protection with *tert*-butyldimethylsilylchloride (TBSCl) and cross-coupling with Me_2Zn-2LiCl furnished the chiral functionalized cyclohex-2enol derivative **132** in 63% yield (Scheme 34).



Scheme 34: Synthesis of chiral precursor molecule **132** *via* CBS reduction of iodocyclohex-2-enone (**130**), TBS protection of the resulting alcohol **131** and cross-coupling with Me_2Zn-2LiCl.

Consequently, **132** was subjected to hydroboration with different boranes at 25 °C. In order to determine both the diastereoselectivity and conversion, an oxidated aliquot was checked by GC analysis. Thereby, di-(*S*)-isopinocampheylborane afforded the highest diastereoselectivity (d.r.= 77:23) (Table 6).

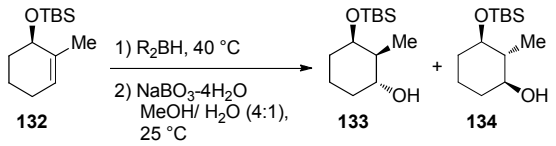
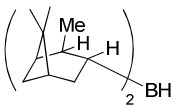
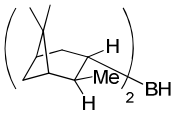
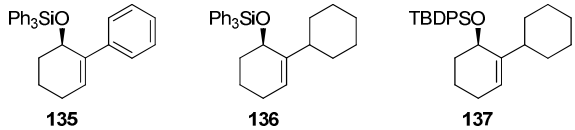


Table 6: Hydroboration of **132** with different boranes; optimization of the diastereoselectivity.

[52] Krafft, M. E. & Cran, J. W. A convenient protocol for the α-iodination of α,β-unsaturated carbonyl compounds with I_2 in an aqueous medium. *Synlett* **8,** 1263-1266 (2005).
[53] overview article: Corey, E. J. & Helal, C. J. Reduction of carbonyl compounds with chiral oxazaborolidine catalysts: a new paradigm for enantioselective catalysis and a powerful new synthetic method. *Angew. Chem. Int. Ed.* **37**, 1986-2012 (1998).

Entry	Boran	Conversion [%]	Diastereoselectivity (133 : 134)
1	 **9-BBN**	0	-:-
2	 **di-(*R*)-isopino-campheylborane**	58	37:63
3	 **di-(*S*)-isopino-campheylborane**	60	77:23

For further increasing the diastereoselectivity, substrates with sterically more challenging protecting groups (PG) and moieties (R) at the double bond were employed (**135**, **136**, **137** in Scheme 35).



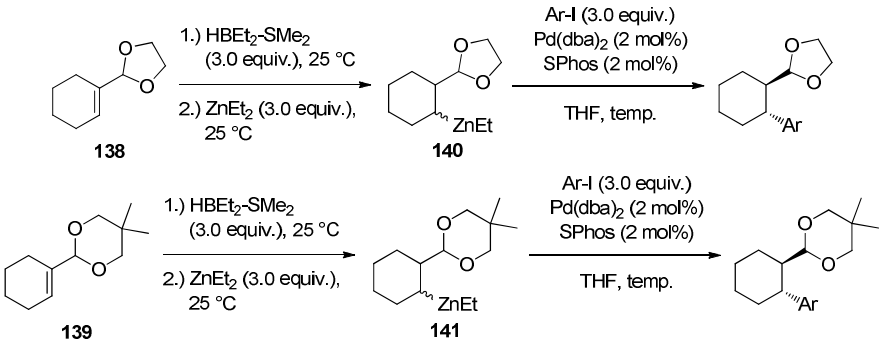
135 **136** **137**

Scheme 35: Sterically hindered substrate for hydroboration with sterically hindered substituents and silyl protecting groups.

The bulkier triphenylsilyl- as well as the *tert*-butyldiphenylsilyl- (TBDPS-)) protecting group and equally the large phenyl- and cyclohexyl moieties were supposed to increase the steric interaction between substrate and hydroborating agent and thus improve the diastereoselectivity. However, **135**, **136** and **137** did not react at all with 9-BBN, with di-(*S*)-isopinocampheylborane or (*S*)-isopinocampheylborane, even at higher temperatures (60 °C) no hydroboration was observed. Since high diastereoselectivity during the hydroboration step is essential for controlling all three stereo centers, this synthetic approach was no longer pursued.

3.2. Investigations with [2-(1,3-Dioxolane-2-yl)cyclohexyl]- and [2-(5,5-Dimethyl-1,3-dioxane-2-yl)cyclohexyl]zinc Compounds

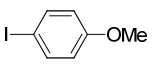
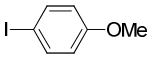
Further investigations should determine whether the stereochemical purity of the cyclohexylzinc reagents has an influence on the diastereoselectivity of the cross-coupling reactions. Therefore, the protected cyclohexenyl derivatives **138** and **139** were transformed via hydroboration followed by boron-zinc exchange using Et_2Zn into the stereodefined ethylzinc compounds **140** and **141** (Scheme 36).



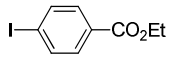
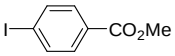
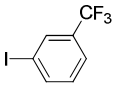
Scheme 36: Hydroboration of **138** and **139** with subsequent boron-zinc exchange and cross-coupling of the freshly generated ethylzinc compounds **140** and **141**.

Subsequently, **140** and **141** were reacted using Pd-catalysis ($Pd(dba)_2$ (2 mol%) and SPhos[54] (2 mol%)) with various aryl iodides (3 equiv.). Cross-couplings of **141** resulted already at room temperature in high diastereoselectivities (d.r.= 98:2; entries 2, 4, 5 and 6 of Table 7). Thereby, it did not make a difference whether an electron-poor or -rich aryl iodide was used (compare entry 2 with entries 5 und 6 of Table 7). However, cross-couplings with **140** as a nucleophile proceeded with significantly lower diastereoselectivities (entries 1 and 3 of Table 7).

Table 7: Pd-catalyzed cross-couplings of the ethylzinc compounds **140** and **141**.

Entry	Zinc Reagent	Aryl Iodide	Temperature [°C] / Time [h]	Yield [%][a] , d.r.[b]
1	**140**		25 / 12	71, 87:13
2	**141**		25 / 12	56, 98:2

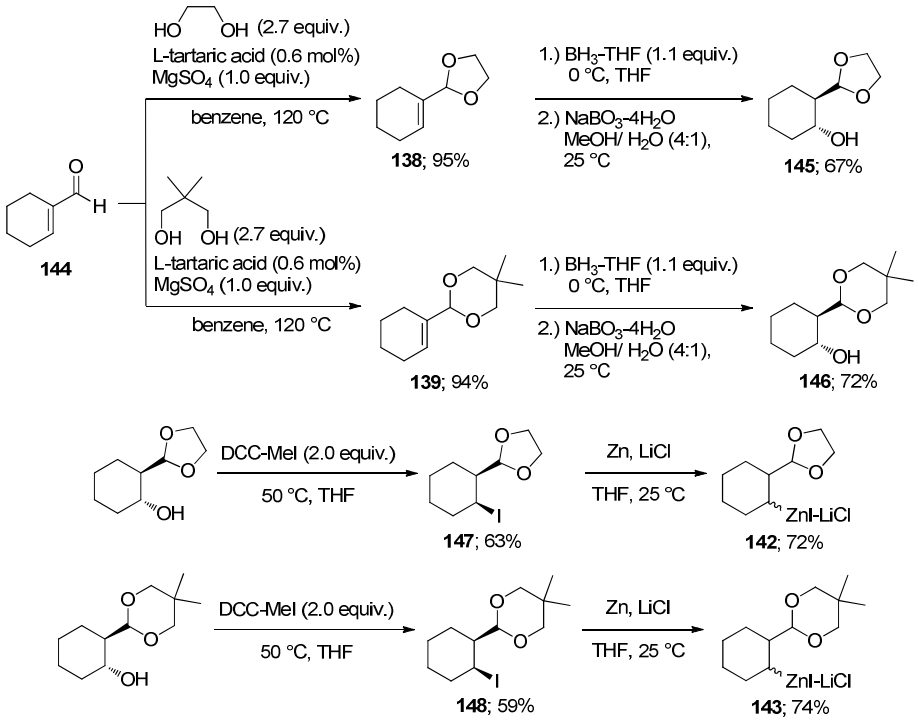
[54] Walker, S. D., Barder, T. E., Martinelli, J. R. & Buchwald, S. L. A rationally designed universal catalyst for Suzuki-Miyaura coupling processes. *Angew. Chem. Int. Ed.* **43**, 1871-1876 (2004).

3	**140**		-10 to 0 / 24	40, 80:20
4	**141**		-10 to 25 / 24	64, 98:2
5	**141**		25 / 12	68, 98:2
6	**141**		25 / 12	67, 98:2

[a] Isolated yield of analytically pure product. [b] Diastereoselectivity determined by capillary GC analysis before and after purification.

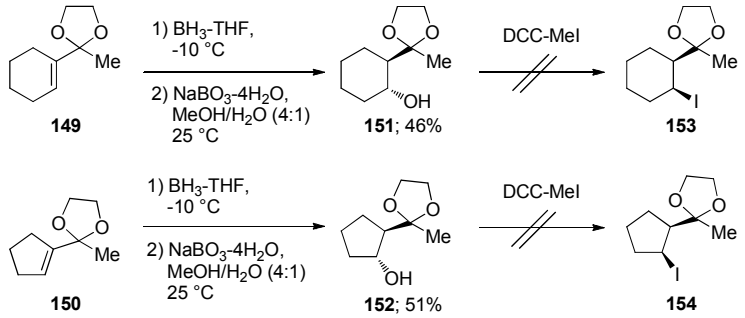
In the following part, the preparation and the cross-couplings of the respective non-stereodefined organozinc iodides (**142**, **143**) will be discussed. 1-Cyclohexen-1-carbaldehyde **144** was therefore protected with the respective diols. The resulting products **138** und **139** were then converted with BH_3-THF and the hydroborated intermediates subsequently oxidized with $NaBO_3$-$4H_2O$ at 0 °C furnishing the corresponding alcohols **145** and **146**. Reaction with dicyclohexylcarbodiimide-iodomethane-complex (DCC-MeI)[55] in THF at 50 °C led to the cyclohexyl iodides **147** und **148**.[56] Subsequent zinc insertion[57] in the presence of LiCl furnished the cyclohexyl iodides **142** and **143** in 72% and 74% yield (Scheme 37).

[55] Scheffold, R. & Saladin, E. Carbodiimidium compounds as reagents in organic chemistry. *Angew. Chem. Int. Ed.* **11**, 229-231 (1972).
[56] H. Stadtmüller, *Dissertation*, Marburg/Lahn **1995**.
[57] Krasovskiy, A., Malakhov, V., Gavryushin, A. & Knochel, P. Efficient synthesis of functionalized organozinc compounds by the direct insertion of zinc into organic iodides and bromides. *Angew. Chem. Int. Ed.* **45**, 1871-6044 (2006).



Scheme 37: Synthesis of [2-(1,3-dioxolan-2-yl)cyclohexyl]- (**142**) und [2-(5,5-dimethyl-1,3-dioxan-2-yl)cyclohexyl]zinc iodide (**143**).

Hydroboration of the ketals **149** and **150** followed by oxidation into the respective alcohols **151** and **152** was successful, whereas the transformation into the corresponding cyclohexyl iodides (**153**, **154**) even with an excess of DCC-MeI and longer reaction times as well as higher reaction temperatures (65 °C) had failed (Scheme 38).



Scheme 38: Attempt to synthesize the cyclohexyl iodides **153** and **154** for subsequent zinc insertion.

142 and **143** were then subjected to Pd-catalyzed cross-coupling reactions with various aryl iodides at different temperatures (Table 8). It showed that the diastereoselectivity depends strongly on the reaction temperature and the nature of the applied aryl iodide. Cross-coupling of **142** and **143** with electron-rich 4-iodoanisole proceeded already at room temperature with relatively high diastereoselectivities (d.r.= 93:7 and 98:2; entry 1 und 2 of Table 8) but lower

yields, whereas cross-coupling with electron-poor aryl iodides (methyl-4-iodobenzoate and 1-iodo-2-(trifluoromethyl)benzene; entries 3, 4, 5 und 6 of Table 8) led to a significantly decreased diastereoselectivity (d.r.= 74:26 to 90:1). Even at -10 °C, cross-couplings of **142** with methyl-4-iodobenzoate und 1-iodo-2-(trifluormethyl)benzene furnished only diastereomeric ratios of 81:19 (entry 3 of Table 8) and 90:10 (entry 5 of Table 8). In contrast, very high diastereoselectivities combined with good yields were obtained when the cross-coupling reactions were carried out at -25 °C (entries 7 to 9 of Table 8).

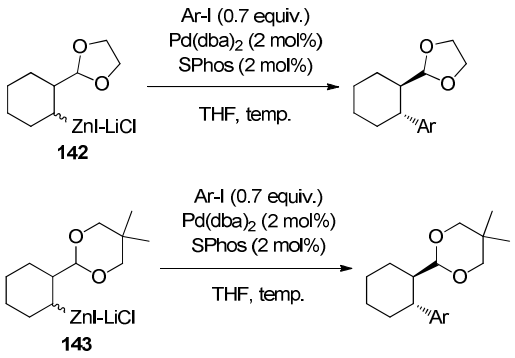
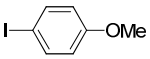
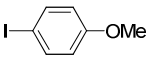
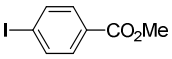
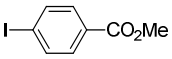
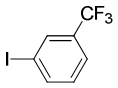
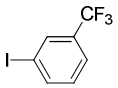
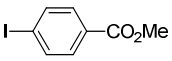
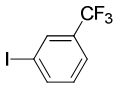


Table 8: Cross-coupling of organozinc iodides **142** und **143** with different aryl iodides.

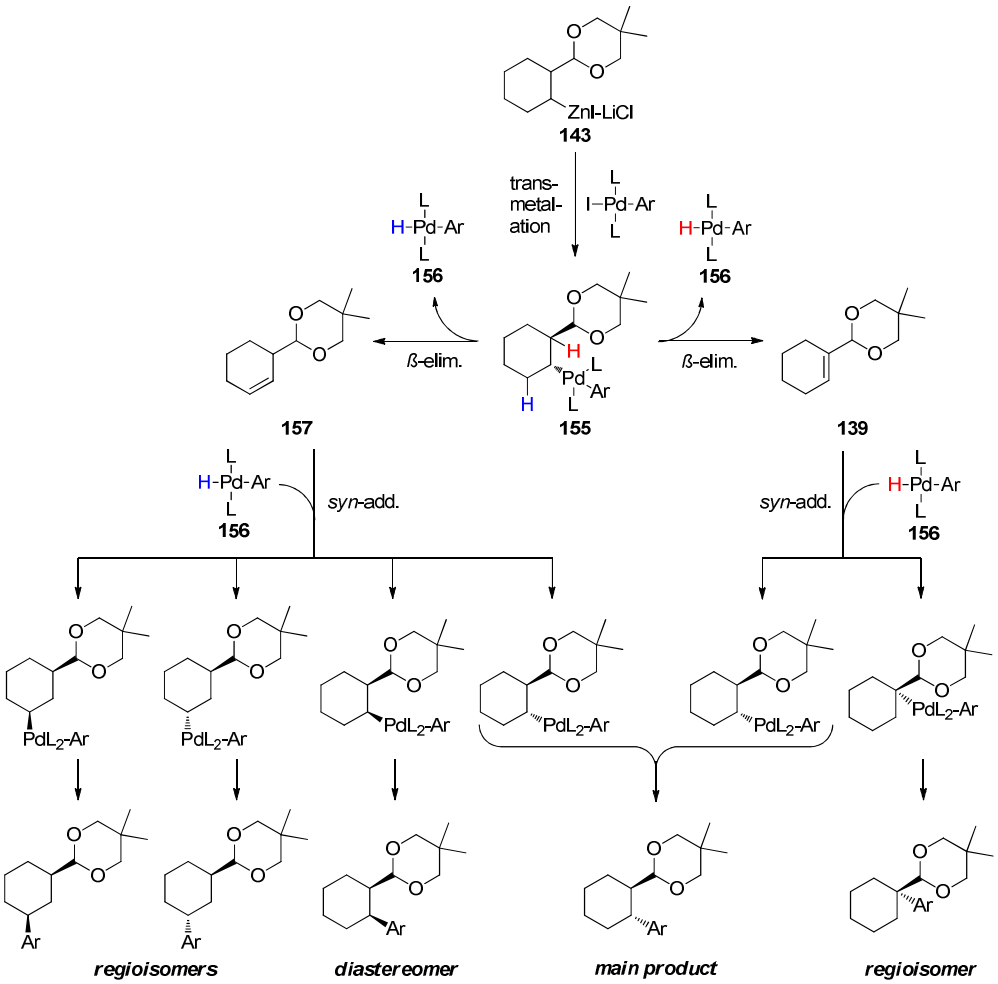
Entry	Zinc Reagent	Aryl Iodide	Temperature [°C] / Time [h]	Yield [%][a] , d.r.[b]	Regio-isomer
1	**142**		25 / 12	44, 93:7	6%
2	**143**		25 / 12	47, 98:2	0%
3	**142**		-10 / 12	60, 81:19	7%
4	**143**		25 / 12	83, 74:26	6%
5	**142**		-10 / 12	79, 90:10	17%[c]
6	**143**		25 / 12	65, 88:12	14%
7	**143**		-25 to -10 / 24	73, >99:1	0%
8	**143**		-25 to -10 / 24	57, >99:1	0%
9	**143**		-25 to -10 / 24	83, >99:1	0%

[a] Isolated yield of analytically pure product. [b] Determined by capillary GC analysis before and after purification. [c] This regioisomer was isolated by column chromatography and analysed.

The observed divergence of diastereoselectivity in the cross-coupling reactions of the organozinc iodides **142** and **143** with electron-poor aryl iodides at higher temperatures is due to a negligible difference in reactivity between the axial and equatorial C-Zn bonds. The formation of regioisomers is due to β-hydride elimination[58] which may occur on the stage of the Pd-intermediate after stereoselective transmetalation (Scheme 39).[59] The fact that regioisomers are not observed with the stereodefined all equatorially substituted organozinc reagents **140** and **141**, which were produced via hydroboration/B-Zn-exchange sequences, suggests that this pathway is restricted to the axially substituted *cis*-configured diastereomer (Probably due to an unstable axial C-Pd bond). β-Hydride elimination may additionally be responsible for the low observed diastereoselectivities (Scheme 39). These results also corroborate the hypothesis presented in **Chapter 2**. The results of the cross-coupling reactions with the cyclohexylzinc reagents **142** and **143** compared to those with the analogous ethylzinc compounds **140** and **141** showed that the latter proceeded already at higher temperatures with excellent diastereoselectivities. This can be attributed to the distinct stereochemistry of the zinc reagents (ZnI vs. ZnEt). While the ethylzinc compounds (**140** and **141**) are stereochemically defined, the organozinc iodides **142** and **143** were employed as diastereomeric mixtures (see **Chapter 2** on the diverse stereochemical behaviour of diastereomeric cyclohexylzinc reagents).

[58] overview article on β-hydride elimination: Lu, X. Control of β-hydride elimination making palladium-catalyzed coupling reactions more diversified. *Topics in Catalysis* **35**, 73-86 (2005).

[59] Thaler, T., Haag, B., Gavryushin, A., Schober, K., Hartmann, E., Gschwind, R., Zipse, H., Mayer, P. & Knochel, P. Highly diastereoselective Csp^3-Csp^2 Negishi cross-coupling with 1,2-, 1,3- and 1,4-substituted cycloalkylzinc compounds. *Nature Chem.* **2**, 125-130 (2010).



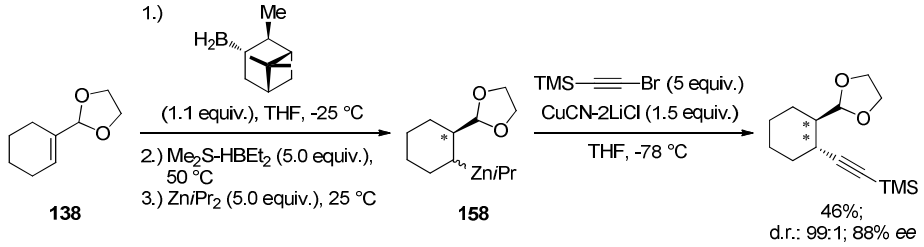
Scheme 39: Formation of regioisomers and diastereomers in the cross-coupling reactions by β-hydride elimination on step of the palladium intermediate **160**.

After β-hydride elimination has taken place the resulting aryl palladium hydride complex **156** has various opportunities for rearrangement to generate cyclohexenes **139** and **157**. The formation of regioisomeric cross-coupling products and their diastereomers could also be observed at temperatures >-25 °C (Table 8).

3.3. Development of an Enantioselective Version of the Diastereoselective Cross-Coupling

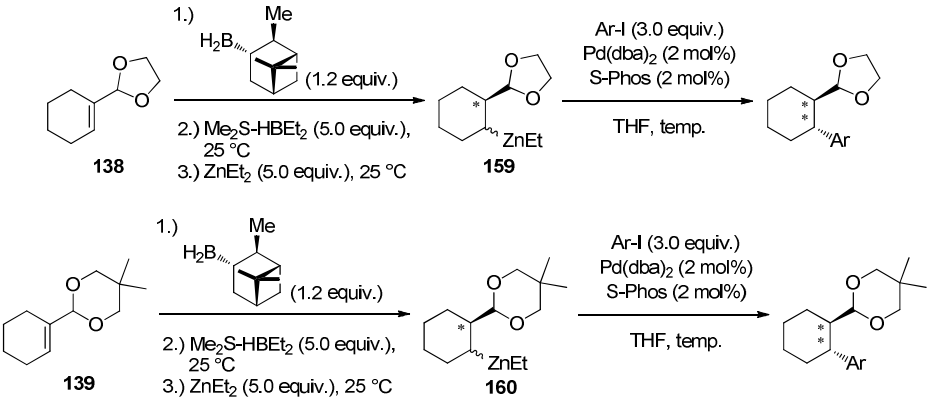
In order to develop an asymmetric version of the diastereoselective cross-coupling reaction of substituted cyclohexylzinc derivatives,[59] a sequence of enantioselective hydroboration followed by B-Zn exchange and eventually Pd-catalyzed cross-coupling was envisioned.

Therefore, a method established by *E. Hupe* and *P. Knochel*[60] was applied. They reacted cyclohexene **138** with (-)-isopinocampheylborane ((-)-IpcBH$_2$) at -10 °C in THF, treated it with an excess of HBEt$_2$ and performed a subsequent boron-zinc exchange with *i*Pr$_2$Zn. The chiral organozinc reagent **158** was trapped *via* Cu(I) mediated alkinylation with high diastereoselectivity (Scheme 40).



Scheme 40: Enantioselective hydroboration, boron-zinc exchange with subsequent Cu mediated alkinylation of the chiral cyclohexylzinc compound **158**.

The chiral cyclohexylzinc compounds **159** and **160** were performed using this method *via* enantioselective hydroboration with subsequent boron-zinc exchange and then subjected to cross-coupling reactions with different aryl iodides (Scheme 41).

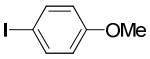
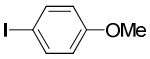
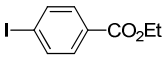
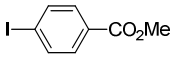
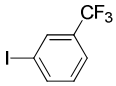


Scheme 41: Synthesis of the chiral cyclohexylzinc reagents **159** und **160** and Palladium catalyzed cross-coupling with aryl iodides.

The respective cross-coupling products were obtained with diastereoselectivities of >99:1 and enantioselectivities of 68 to 81% *ee* (Table 9). This method allows the direct and stereoselective approach to functionalized 1,2-disubstituted cyclohexanes.

[60] Hupe, E. & Knochel, P. Formal enantioselective Michael addition with umpolung of reactivity. *Angew. Chem. Int. Ed.* **40**, 3022-3025 (2001).

Table 9: Cross-coupling of the chiral ethylzinc reagents **159** und **160**.

Entry	Zinc Reagent	Aryl Iodide	Temperature [°C] / Time [h]	Yield [%][a] , d.r.[b]	*ee* [%][c]
1	**159**		25 / 12	39, >99:1	n. d.
2	**160**		25 / 12	82, >99:1	73
3	**159**		-5/ 12	32, >99:1	n. d.
4	**160**		-10 to 0 / 24	82, >99:1	81
5	**160**		-10 to 0 / 24	54, >99:1	77
6	**160**		-10 to 0 / 24	52, >99:1	68

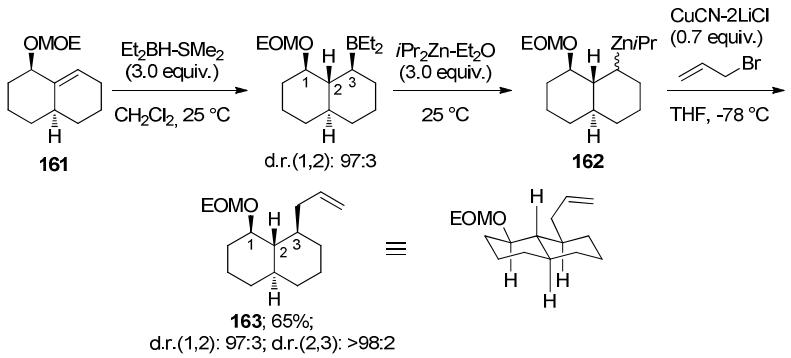
[a] Isolated yield of analytically pure product. [b] Diastereoselectivity determined by capillary GC analysis before and after purification. [c] Enantioselectivity.

3.4. Cross-Coupling with [8-(Ethoxymethoxy)decahydronaphthalen-1-yl](ethyl)zinc

E. Hupe und *P. Knochel* showed that decahydro-1-naphthalenol **166** can be highly diastereoselectively functionalized via hydroboration, boron-zinc exchange and subsequent allylation (Scheme 42).[61] Thus, two stereocentres (2 and 3) can be introduced into the molecule at the same time. Via hydroboration it is possible to determine the relative configuration between the two stereocentres ***1*** and ***2***. In his thesis, *E. Hupe* points out that the choice of alcohol-protecting groups as well as the choice of solvent during the hydroboration step are crucial for achieving high diastereoselectivities.[62] The Cu-mediated allylation of the organozinc compound **162**, which is generated via boron-zinc exchange, is highly stereoselective and forms the stereocentre 3 with a d.r. (rel. conf. of positions *2*,*3*) >98:2. In the final product **163**, all substituents of the cyclohexyl ring of the *trans*-configured decahydro-1-naphthalenol occupy equatorial positions. Thus, the thermodynamically most stable product is formed.

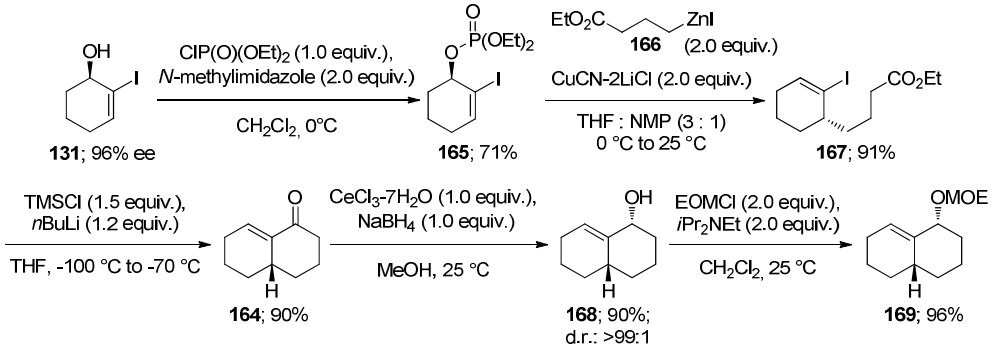
[61] a) Boudier, A., Hupe, E. & Knochel, P. Highly diastereoselective synthesis of monocyclic and bicyclic secondary diorganozinc reagents with defined configuration. *Angew. Chem. Int. Ed. Engl.* **39**, 2294-2297 (2000); b) Hupe, E., Calaza, M. I. & Knochel, P. Substrate-controlled highly diastereoselective synthesis of primary and secondary diorganozinc reagents by a hydroboration/boron-zinc exchange sequence. *Chem. Eur. J.* **9**, 2789-2796 (2003).

[62] E. Hupe, *Dissertation*, München **2002**.



Scheme 42: Synthesis of decahydronaphthalenylzinc reagent **162** and stereoselective functionalization *via* Cu-mediated allylation; selective synthesis of the thermodynamically most stable products.

We were then wondering if it was possible to achieve similar high diastereoselectivities by cross-coupling the decahydronaphthalenylzinc compound **162** with aryl iodides. Therefore, hexahydronaphthalenone (**164**) was synthesized starting from the chiral alcohol **131** which was transformed in the first step with diethylchlorophosphate to the phosphate **165**. A subsequent S_N2' reaction with the functionalized organozinc compound **166** led to the ester **167**, which was cyclized after iodine-lithium exchange to give compound **164** (Scheme 43).[63]



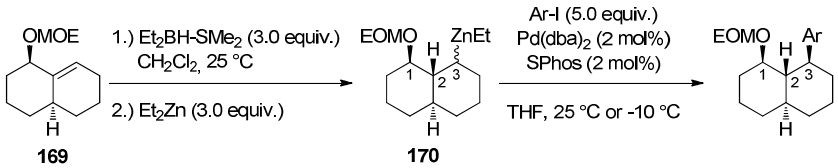
Scheme 43: Synthesis of EOM-protected decahydronaphthalenol derivative **169**.

Following, **164** was diastereoselective reduced via *Luche*-reduction[64] to the alcohol **168** and protected with ethoxymethyl chloride (EOMCl). Then, according to the procedure described by *E. Hupe et al.*, **169** was subjected to hydroboration with Et_2BH-SMe_2 complex in CH_2Cl_2 followed by a boron-zinc exchange with Et_2Zn.[61] The resulting organozinc compound **170**

[63] Calaza, M. I., Hupe, E. & Knochel, P. Highly *anti*-selective S_N2' substitutions of chiral cyclic 2-iodo-allylic alcohol derivatives with mixed zinc-copper reagents. *Org. Lett.* **5**, 1059-1061 (2003).

[64] Gemal, A. L. & Luche, J.-L. Lanthanoids in organic synthesis. 6. The reduction of α-enones by sodium borohydride in the presence of Lanthanoid chlorides: synthetic and mechanistic aspects. *J. Am. Chem. Soc.* **103**, 5454-5459 (1981).

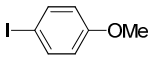
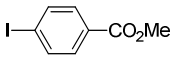
was used in Pd-catalyzed cross-coupling with 4-iodoanisole and methyl-4-iodobenzoate (Scheme 44).



Scheme 44: Synthesis of [8-(ethoxymethoxy)decahydronaphthalen-1-yl](ethyl)zinc (**170**) and subsequent cross-coupling.

The results are summarized in Table 10. The conversion of the reaction was low and the diastereoselectivity moderate. Hydroboration provided a diastereoselectivity of 90:10, whereas in the cross-coupling reactions significantly lower selectivities (d.r.= 67:33 and 85:15) were achieved. In order to check whether the correct reaction conditions were used, the allylation of Scheme 42 was repeated. The allylation product **163** was isolated with a yield of 57% (lit.: 65%) and diastereoselectivities of d.r.(1,2) 97:3 and d.r.(1,3) >98:2 (lit.: 97:3 and >98:2). Thus, reproduction of the reaction was successful.

Table 10: Pd-catalyzed cross-coupling with [8-(ethoxymethoxy)decahydronaphthalen-1-yl](ethyl)zinc (**170**).

Entry	Zinc Reagent	Aryl Iodide	Temperature [°C]	d.r.(1,2); d.r.(1,3)[a]	Yield[%][b]
1	**170**		25	90:10; 67:33	n. i.
2	**170**		-10	91:9; 85:15	31

[a] Diastereoselectivity determined by capillary GC analysis before and after purification. [b] Isolated yield of analytically pure product.

4. Highly Diastereoselective Arylations of Substituted Piperidines

4.1. Introduction

Substituted piperidines are ubiquitous structural motifs present in numerous bioactive alkaloids.[65] In order to ensure appropriate biological activity, many of them have to be prepared in a stereodefined manner.[65] Therefore, the development of efficient methods for the diastereoselective construction of piperidines bearing more than one stereocenter represents an important synthetic task.[66] Still, procedures for the direct stereoselective arylation of the

[65] (a) de Risi, C., Fanton, G., Pollini, G. P., Trapella, C., Valente, F. & Zanirato, V. Recent advances in the stereoselective synthesis of *trans*-3,4-disubstituted-piperidines: applications to (-)-paroxetine. *Tetrahedron: Asymmetry* **19**, 131-155 (2008); (b) Escolano, C., Amat, M. & Bosch, J. Chiral oxazolopiperidone lactams: versatile intermediates for the enantioselective synthesis of piperidine-containing natural products. *Chem. Eur. J.* **12**, 8198-8207 (2006); c) Buffat, M. G. P. Synthesis of piperidines. *Tetrahedron* **60**, 1701-1729 (2004); (d) Felpin, F.-X. & Lebreton, J. Recent advances in the total synthesis of piperidine and pyrrolidine natural alkaloids with ring-closing metathesis as a key step. *Eur. J. Org. Chem.*, 3693-3712 (2003); (e) Laschat, S. & Dickner, T. Stereoselective synthesis of piperidines. *Synthesis* **13**, 1781-1813 (2000); (f) Bailey, P. D., Millwood, P. A. & Smith, P. D. Asymmetric routes to substituted piperidines. *Chem. Commun.*, 633-640 (1998).

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piperidine ring are scarce.[67] Only one isolated example of the diastereoselective coupling of a 6-methylpiperidin-2-yl organometallic with 4-bromoveratrole furnishing the *trans*-2,6-disubstituted product has been reported.[67c] So far the direct stereoselective synthesis of 2,4- and 2,5-disubstituted arylated piperidines via Csp^3-Csp^2 cross-coupling remains a challenging problem. Recently, a highly diastereoselective couplings of several substituted cycloalkyl derivatives mediated by Pd was reported.[68] Herein, we show that Pd-catalyzed cross-couplings can be efficiently used for a highly diastereoselective preparation of various disubstituted or annulated piperidines.

4.2. Results and Discussion

It was previously demonstrated that cross-couplings of substituted cyclohexylzinc reagents with diverse aryl halides result in the stereoconvergent formation of the thermodynamically

sequential cross-metathesis-cationic cyclisation. *Adv. Synth. Catal.* **349**, 157-160 (2007); (r) Cortez, G. A., Schrock, R. R. & Hoveyda, A. H. Efficient enantioselective synthesis of piperidines through catalytic asymmetric ring-opening/cross-metathesis reactions. *Angew. Chem. Int. Ed.* **46**, 4534-4538 (2007); (s) Amat, M., Bassas, O., Llor, N., Cantó, M., Pérez, M., Molins, E. & Bosch, J. Dynamic kinetic resolution and desymmetrization processes: a straightforward methodology for the enantioselective synthesis of piperidines. *Chem. Eur. J.* **12**, 7872-7881 (2006); (t) Kauffman, G. S., Watson, P. S. & Nugent, W. A. Strategy for the enantioselective synthesis of *trans*-2,4-disubstituted piperidines: application to the CCR3 Antagonist IS811. *J. Org. Chem.* **71**, 8975-8977 (2006); (u) Takemiya, A. & Hartwig, J. F. Rhodium-catalyzed intramolecular, anti-Markovnikov hydroamination. Synthesis of 3-arylpiperidines. *J. Am. Chem. Soc.* **128**, 6042-6043 (2006); (v) Peltier, H. M. & Ellman, J. A. *N*-Sulfinyl metalloenamine conjugate additions: asymmetric synthesis of piperidines. *J. Org. Chem.* **70**, 7342-7345 (2005); (w) Poerwono, H., Higashiyama, K., Yamauchi, T., Kubo, H., Ohmiya, S. & Takahashi, H. Stereocontrolled preparation of *cis*- and *trans*-2,6-dialkylpiperidines via diastereoselective reaction of 1-aza-4-oxabicyclo[4.3.0]nonane derivatives with Grignard reagents. *Tetrahedron* **54**, 13955-13970 (1998).

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favoured arylpalladium intermediates which after reductive elimination afford the desired arylated products with retention of configuration (d.r. up to >99:1).[68] Due to the structural importance of piperidines, we have envisioned the performance of diastereoselective cross-couplings with the related substituted piperidinylzinc compounds. By exploiting the pseudo-allylic strain induced by the protecting group at the N,[69] we were able to prepare both the *cis*- and *trans*-2,4-disubstituted piperidine derivatives with excellent levels of diastereoselectivity.

First, we have generated various piperidin-2-ylzinc reagents of type **1** starting from the respective piperidines **172a-e** according to the procedures of *Beak and Lee*[70] and *Coldham and Leonori*.[67c] To our delight, the Pd-catalyzed cross-coupling of **171a-e** with various aryl and heteroaryl iodides using 2% SPhos[71] or 5% RuPhos[72] and 2-5% $Pd(dba)_2$ as catalyst system furnished the desired α-arylated products **173** in 54-84% yield and with an exceptional level of diastereoselectivity (d.r. of 95:5 to >99:1; Table 11). Thus, cross-coupling of the 4-methyl-substituted piperidinylzinc reagent **171a** with electron-rich 4-iodoanisole using 2% $Pd(dba)_2$ and 2% SPhos at 55 °C furnished exclusively the *cis*-configured product **173a** in 78% yield (entry 1of Table 11).[73]

[69] (a) Paulsen, H. & Todt, K. Magnetic anisotropy of the amide group. *Angew. Chem. Int. Ed. Engl.* **5**, 899-900 (1966); (b) Johnson, R. A. Conformations of alkylpiperidine amides. *J. Org. Chem.* **33**, 3627-3632 (1967).

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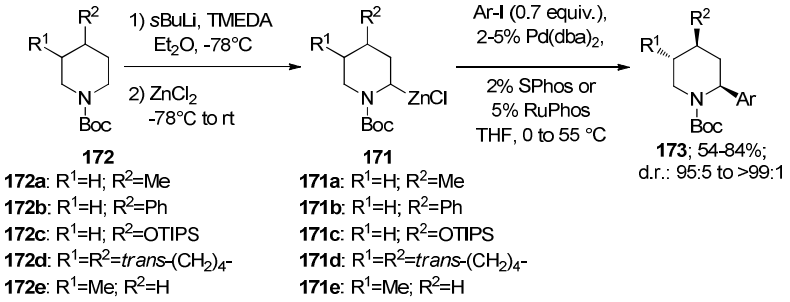
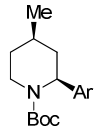
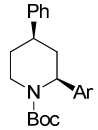
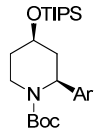
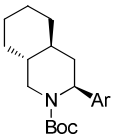
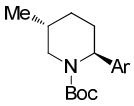
[73] The relative configurations of **173d** and **173h** were directly determined via X-ray analysis. The relative configurations of **173n** and **173q** were determined via acidic removal of the Boc-protective group and subsequent tosylation. The crystals of the tosylates (**173na** and **173qa**) proved suitable for X-ray analysis. See supporting information for details.



172
172a: R^1=H; R^2=Me
172b: R^1=H; R^2=Ph
172c: R^1=H; R^2=OTIPS
172d: R^1=R^2=*trans*-$(CH_2)_4$-
172e: R^1=Me; R^2=H

171
171a: R^1=H; R^2=Me
171b: R^1=H; R^2=Ph
171c: R^1=H; R^2=OTIPS
171d: R^1=R^2=*trans*-$(CH_2)_4$-
171e: R^1=Me; R^2=H

Table 11: Diastereoselective cross-coupling of substituted piperidin-2-ylzinc reagents.

Entry		Product	Yield [%][a]	d.r.[b]
1		**173a**: Ar: 4-MeO-C_6H_4	78	>99:1[c]
2		**173b**: Ar: 4-F_3C-C_6H_4	81	95:5[c]
3		**173c**: Ar: 3-Cl-C_6H_4	76	96:4[c]
4		**173d**: Ar: 3-NC-C_6H_4	64	97:3[c]
5		**173e**: Ar: 4-EtO_2C-C_6H_4	67	98:2[c]
6		**173f**: Ar: 4-pyridinyl	73	95:5[c]
7		**173g**: Ar: 4-F_3C-C_6H_4	64	97:3[d]
8		**173h**: Ar: 4-NC-C_6H_4	79	>99:1[d]
9		**173i**: Ar: 4-MeO_2C-C_6H_4	67	99:1[d]
10		**173j**: Ar: 4-EtO_2C-C_6H_4	84	97:3[e]
11		**173k**: Ar: 4-F-C_6H_4	83	95:5[e]
12		**173l**: Ar: 4-F_3C-C_6H_4	81	95:5[e]
13		**173m**: Ar: 4-NC-C_6H_4	81	97:3[e]
14		**173n**: Ar: 4-F_3C-C_6H_4	69	>99:1[d]
15		**173o**: Ar: 4-NC-C_6H_4	54	>99:1[d]
16		**173p**: Ar: 4-MeO-C_6H_4	60	97:3[d]
17		**173q**: Ar: 4-NC-C_6H_4	62	96:4[d]
18		**173r**: Ar: 4-EtO_2C-C_6H_4	59	95:5[d]

[a] Isolated yield. [b] Determined by GC and/or $^1H/^{13}C$ NMR analysis. [c] 2% $Pd(dba)_2$, 2% SPhos, THF, 55 °C, 12 h. [d] 5% $Pd(dba)_2$, 5% RuPhos, THF, 55 °C, 12 h. [e] 5% $Pd(dba)_2$, 5% RuPhos, THF, 55 °C, 60 h. [f] 5% $Pd(dba)_2$, 5% RuPhos, THF, 0 °C (6 h), then rt (12 h), then 40 °C (12 h).

Coupling of **171a** with electron-poor aryl iodides and 4-iodopyridine under the same conditions gave the products **173b-f** with d.r. from 95:5 to 98:2 (entries 2-6). The piperidinylzinc reagent **171b** bearing a large phenyl ring instead of the smaller methyl substituent provided, under slightly altered conditions (5% $Pd(dba)_2$ and 5% RuPhos at 55 °C), the *cis*-products **173g-i** with comparable yields (64-79%) and equally high

diastereoselectivities (97:3 to >99:1; entries 7-9). Even the functionalized piperidinylzinc reagent **171c** bearing an OTIPS (OSi(*i*-Pr)$_3$) group in position 4 reacted smoothly furnishing the *cis*-α-arylated products **173j-m** with high yields (81-84%) and d.r. between 95:5 and 97:3 (entries 10-13). The method also proved applicable to the *trans*-decahydroisoquinolinyl scaffold. By using the method of *Beak and Lee*[70] we were able for the first time to regioselectively metalate this heterocycle at position 3. Cross-coupling of the resulting organozinc species **171d** led to the stereodefined 2,4,5-trisubstituted products **173n-p** in 54-69% yield with excellent d.r. (97:3 to >99:1; entries 14-16). In the case of the 5-methyl-substituted reagent **171e**, lower temperatures were necessary for achieving high diastereoselectivities (Table 11). Thus, the *trans*-2,5-disubstituted products **173q-r** were obtained in moderate yields of 59-62% with a high d.r. of 95:5 (entries 17-18).

Complementary to the diastereoselective preparation of the *cis*-2,4-disubstituted piperidines, we also report the synthesis of the corresponding *trans*-isomers by switching the positions of the substituent and the C-Zn bond. Thus, in preliminary experiments, we have prepared the 2-substituted piperidin-4-ylzinc reagent **174a** via LiCl-promoted Zn-insertion into the iodide **175a**[74] and subjected it to cross-coupling with 4-iodobenzonitrile and iodobenzene using 5% $TMPP_2PdCl_2$[75] as catalyst (Table 12).[68] The *trans*-coupling products **176a-b** were obtained in 50-74% yield with diastereoselectivities of d.r.: 91:9 and 92:8 (entries 1 and 2 of Table 12).[76] By examining the NMR spectra of the *N*-Boc protected products **176a** and **176b**, we found that both revealed the presence of two Boc-conformers at room temperature. These findings are supported by DFT-analysis.[77] The calculations also confirmed the presence of two energetically close chair and twist-boat conformers whose existence may be responsible for the observed non-perfect diastereoselectivity. Furthermore, X-ray structures of the already prepared *N*-Boc protected piperidines **173d** and **173h**[73] (entries 4 and 8 of Table 11) showed a twisted ring conformation, whereas the structures of the *N*-Ts protected piperidines **173na** and **173qa**[73] displayed an almost perfect chair-like structure. We, therefore, prepared the corresponding *N*-tosylated zinc reagent **174b**. Cross-coupling of **174b** with 4-iodobenzonitrile

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[76] The relative configuration of **176a** was determined via acidic removal of the Boc-protective group and subsequent tosylation. The crystals of the tosylate proved suitable for X-ray analysis. The relative configurations of **176c** and **176e** were directly determined via X-ray analysis. See supporting information for details.

[77] ^{1}H and ^{13}C NMR analyses of **176a** and **176b** at 70 °C showed an average spectrum of the two conformers. This finding is supported by a conformational analysis of product **176b** at the B3LYP / 6-31 G (d,p) level. See the Supporting Information for details.

under the same reaction conditions led to the *exclusive formation* of the *trans*-isomer **176c** in 70% yield (entry 3). Remarkably, the couplings of the zinc reagent **174c** bearing only a small methyl group in position 2 also gave the respective *trans*-isomers **176e-f** with an excellent diastereoselectivity of d.r.: 97:3 (entries 5 and 6).

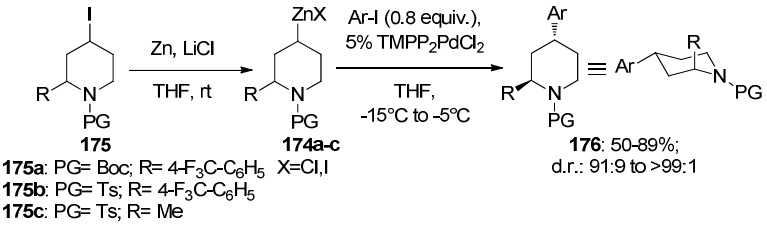


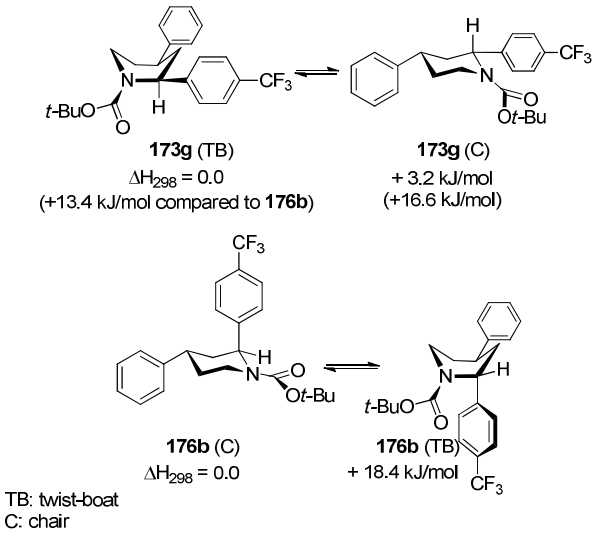
Table 12: Diastereoselective cross-coupling of 2-substituted piperidin-4-ylzinc reagents.

Entry	Product	Yield [%][a]	d.r.[b]
1	**176a:** Ar: 4-NC-C_6H_4	74	91:9
2	**176b**: Ar: Ph	50	92:8
3	**176c**: Ar: 4-NC-C_6H_4	70	>99:1
4	**176d**: Ar: 4-MeO_2C-C_6H_4	69	96:4
5	**176e**: Ar: 4-NC-C_6H_4	84	97:3
6	**176f**: Ar: 4-MeO_2C-C_6H_4	89	97:3

[a] Isolated yield. [b] Determined by GC and/or $^1H/^{13}C$ NMR analysis.

In order to explain the distinct stereochemical outcome of these couplings, the *cis*/*trans* stability differences between **173g** and **176b** together with the respective data for the Zn- and Pd-intermediates were analyzed at the B3LYP/631SVP level (Scheme 44 and Table 13).[78] From our former studies,[68] it was clear that the relative stabilities of the Pd-intermediates represent the crucial factor for the determination of the final diastereoselectivity of the cross-coupling.

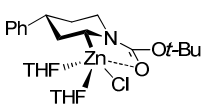
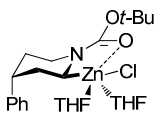
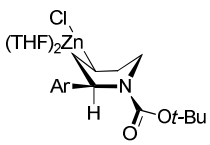
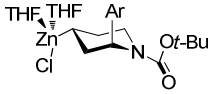
[78] The theoretical methods used herein are identical to those in ref 68 and involved the combination of the B3LYP hybrid functional with the def2-SVP all-electron basis set for Zn, the ECP-based def2-SVP basis set for Pd,[21] and the 6-31G(d,p) basis set for all other elements.

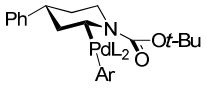
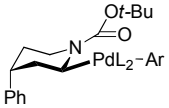
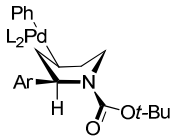
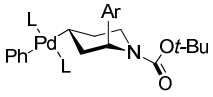


Scheme 44: DFT-conformational analysis of *cis*-isomer **173g** and *trans*-isomer **176b**.

The stabilities of the products (**173g** and **176b**) and of the corresponding zinc intermediates have been calculated in order to refine our mechanistic picture. In contrast to the corresponding cyclohexanes, in which an overall equatorial substitution pattern is thermodynamically preferred,[68] the pseudo-allylic strain in *N*-Boc piperidines caused by the partial double-bond character of the amide bond forces the substituent vicinal to the nitrogen into an axial orientation.[69] Therefore, *cis*-isomer **173g** was found to be significantly less stable (by 13.4 kJ/mol) than *trans*-isomer **176b**. Detailed DFT conformational analysis (chair vs. twist boat) shows that the energy difference between the chair and twist-boat conformation is negligible for **173g**, whereas it is large for **176b** thus confirming our observations on **176a** and **176b** by ^{1}H and ^{13}C NMR spectroscopy.

Table 13: DFT calculation-based conformational analysis on the diastereomeric Zinc and Palladium complexes.

Entry	**Zn- and Pd-Intermediates[a], $\Delta H^{298}_{ax\text{-}eq}$ (kJ/mol)[b]**	
	 ***eq*-171b** (C)	 ***ax*-171b** (C)
1	+15.4	
	 ***eq*-174a** (TB)	 ***ax*-174a (C)**
2	-8.4	

	 ***eq*-177** (C)	 ***ax*-177** (C)
3	+15.0	
	 ***eq*-178** (TB)	 ***ax*-178** (C)
4	-8.6	

[a] Ar: 4-F_3C-C_6H_4. Preferred conformations are indicated as twist-boat (TB) or chair (C). [b] Calculated energetic differences (B3LYP/631SVP) between the thermodynamically lowest conformers of the two diastereomers; L: PMe_3.

The stabilities of the respective Pd- and Zn-intermediates involved in the formation of the cross-coupling products **173g** and **176b** have been calculated using the same model as in our recent study of the analogous cyclohexyl systems.[68] Whereas the diastereomeric substituted cyclohexylzinc complexes possessed very similar energies, large differences in the stabilities of the corresponding piperidinylzinc species were found. In the case of piperidin-2-ylzinc reagent **171b**, the equatorial orientation of the C-Zn bond is stabilized by its coordination to the carbonyl oxygen atom of the Boc group leading to a pentacoordinated Zn-center. This results in an energetic preference for **eq-171b** by 15.4 kJ/mol (entry 1 of Table 13). Since pseudo-allylic strain in the 4-zincated piperidinyl species **174a** dictates an axial position of the substituent at C2, axial orientation of the C-Zn bond is hampered by 1,3-diaxial repulsions resulting in **ax-174a** as the most stable conformer (entry 2). This underlines the "*Janus-like*" nature of the Boc-group showing its sterically demanding, repulsive character towards vicinal substituents, yet turning into an electrostatically attractive neighbor with Lewis-acidic metal centers present at the same position. Analogously to the cyclohexyl systems, the Pd moiety shows a preference for the equatorial position in all cases. In the piperidin-2-ylpalladium intermediates (**eq-177** and **ax-177**; entry 1), in which the square-planar coordination sphere of Pd is not perturbed, this natural preference is magnified by a close contact between the Pd-center and the carbonyl oxygen atom of the Boc group. If, however, C2 is occupied by an aryl/alkyl substituent, 1,3-allylic strain[69] takes effect and causes axial orientation (**ax-178** vs. **eq-178**; entry 2). Without this interaction, diaxial repulsions dictate equatorial orientation of the aryl/alkyl substituent (**eq-177** vs. **ax-177**; entry 1).[68] Considering the energetic differences of the organometallic intermediates, the diastereoselectivity in the couplings of the

piperidinylzinc reagents (**171** and **174**) may be determined both on the stage of the respective Zn- as well as Pd-complexes. In the case of the couplings of the piperidin-2-ylzinc chlorides (**171**), there is strong evidence that the diastereoselectivity may already be introduced into the molecule via the lithiation step.[67c,f,g,70] For the piperidin-4-ylzinc iodides (**174**), the stereoselectivity is most likely introduced via a selective transmetalation step between the Zn-reagent and the aryl-Pd complex leading to the thermodynamically most stable intermediate, as proposed in **Chapter 2**.

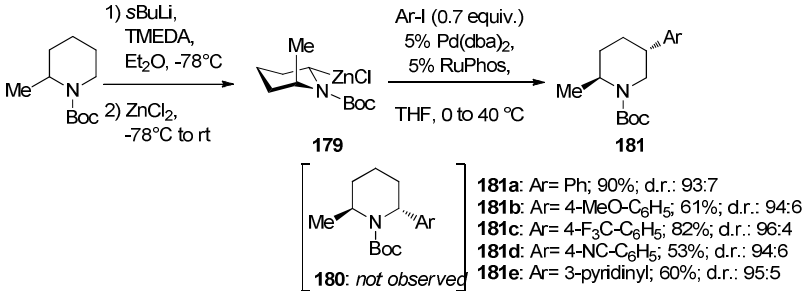
In continuation of our study, we found that arylations with the 6-methyl-substituted piperidin-2-ylzinc reagent **179** in the presence of $Pd(dba)_2$/RuPhos[72] as catalyst system consistently resulted in the highly stereoselective formation of the 5-arylated *trans*-configured products of type **181** (d.r.: 93:7 to 96:4),[79] whereas the expected *trans*-2,6-disubstituted products (**180**)[67c] were not obtained (Scheme 45). It is noteworthy that the coupling proceeded equally well with electron-rich (**181b**) and electron-poor aryl iodides (**181c-e**). We assume that this reaction proceeds via β–hydride elimination of the Pd moiety.[80] The resulting $ArPdL_2H$[81] complex stays bound to the same side of the tetrahydropyridinyl ring and its subsequent *syn*-addition[82] places the Pd in the sterically less hindered position 5. Rapid reductive elimination furnishes the observed δ-arylated 2,5-disubstituted coupling products (**181**). This Pd 1,2-migration/ cross-coupling sequence seems to be a function of the nature and stoichiometry of the phosphine ligand. In our case, a Pd/ RuPhos ratio of 1:1 was used. Coldham and Leonori[67c] reported the use of $Pd(OAc)_2$/ tBu$_3$P with a ratio of 1:2 as the catalyst system, which may lead to a better stabilization of Pd(0) and thus prevent β-hydride elimination.

[79] The relative configuration of **181c** was determined via acidic removal of the Boc protecting group and subsequent tosylation. The crystals of the tosylate proved suitable for X-ray analysis.

[80] (a) Ogawa, R., Shigemori, Y., Uehara, K., Sano, J., Nakajima, T. & Shimizu, I. Enantioselective elimination of Pd-H from η^3-allylpalladium-Tol BINAP complexes. evidence of syn elimination pathway. *Chem. Lett.* **36**, 1338-1339 (2007); (b) Lloyd-Jones, G. C. & Slatford, P. A. Unusually large $^2H/^1H$ kinetic isotope effects accompanying a syn-β-H elimination reaction in a σ-alkyl-palladium complex. *J. Am. Chem. Soc.* **126**, 2690-2691 (2004) and references therein.

[81] (a) Hills, I. D. & Fu, G. C. Elucidating reactivity differences in palladium-catalyzed coupling processes: The chemistry of palladium hydrides. *J. Am. Chem. Soc.* **126** 13178-13179 (2004); (b) Grushin, V. V. Hydrido complexes of palladium. *Chem. Rev.* **96**, 2011-2033 (1996); (c) Heck, R. F. Palladium-catalyzed reactions of organic halides with olefins. *Acc. Chem. Res.* **12**, 146-151 (1979).

[82] (a) Schmidt, A. F. & Smirnov, V. V. The mechanism of the palladium hydride β-elimination step in the Heck reaction. *Kinet. Catal.* **44**, 518-523 (2003); (b) Henry, P. M. & Ward, G. A. Stereochemistry of phenylpalladation of cyclohexene. *J. Am. Chem. Soc.* **94**, 673-674 (1972).



Scheme 45: Pd-1,2-migration in the diastereoselective cross-coupling of *N*-Boc 6-methylpiperidin-2-ylzinc chloride.

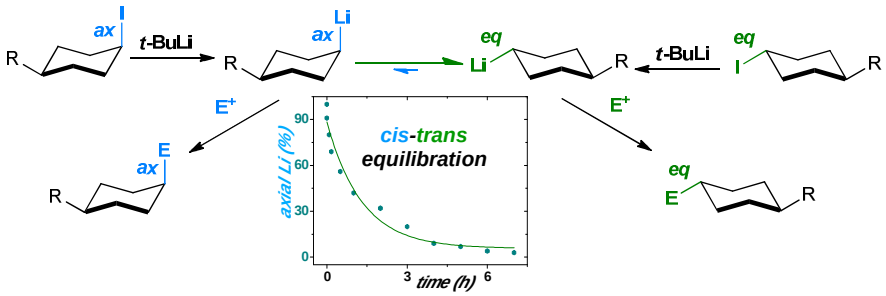
5. Summary and Outlook

This work dealt with both the investigation and applications of the distinct stereochemical behaviours of carbon-metal bonds. Therefore, a novel practical access to stereodefined C-Li bonds was established via a stereoretentive I-Li exchange on cyclohexyl iodides which allowed a thorough examination of their configurational stabilities and the stereochemistry of their quenching with various electrophiles. Mechanistic studies on the configurational stability of the C-Zn bond in substituted cyclohexylzinc reagents showed that distinct stereochemical pathways are responsible for the observed stereoconvergence in the diastereoselective Pd-catalyzed cross-couplings. Thereby, the equatorial C-Zn bond reacts with retention and the axial C-Zn bond with inversion of its stereoconfiguration under suitable reaction conditions. The highly diastereoselective Pd-catalyzed cross-coupling methodology was extended to functionalized cyclohexyl derivatives and an enantio- and diastereoselective method for the preparation of chiral arylated functionalized cyclohexanes was developed. Highly diastereoselective cross-coupling was also established for piperidinylzinc derivatives. Selective access to both the *cis*- and *trans*-2,4-disubstituted piperidine derivatives was enabled.

5.1. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted Cyclohexyllithium Derivatives

Although the stereoselective generation and stereochemistry of α-heteroatom-substituted alkyl-, benzylic and allylic organolithium reagents are well studied, the stereoselective preparation of non-stabilized secondary alkyllithiums has remained a major synthetic challenge. A practical stereoretentive synthesis to unstabilized stereodefined cyclohexyllithium reagents from the readily available organic iodides via I-Li exchange has been presented in this work. Using this approach a detailed study on the configurational stabilities, stereochemical behaviour and reactivities of various axially and equatorially substituted cyclohexyllithium reagents was performed. Thus, the stereochemical paths (S_E2 vs. S_i2) of the quenching reactions were shown to depend on the respective cyclohexyllithium diastereomer and the electrophile. In all cases, the axial cyclohexyllithium was found to almost completely equilibrate into the configurationally stable, equatorial diastereomer. This inversion process was followed for differently substituted cyclohexyllithiums over time

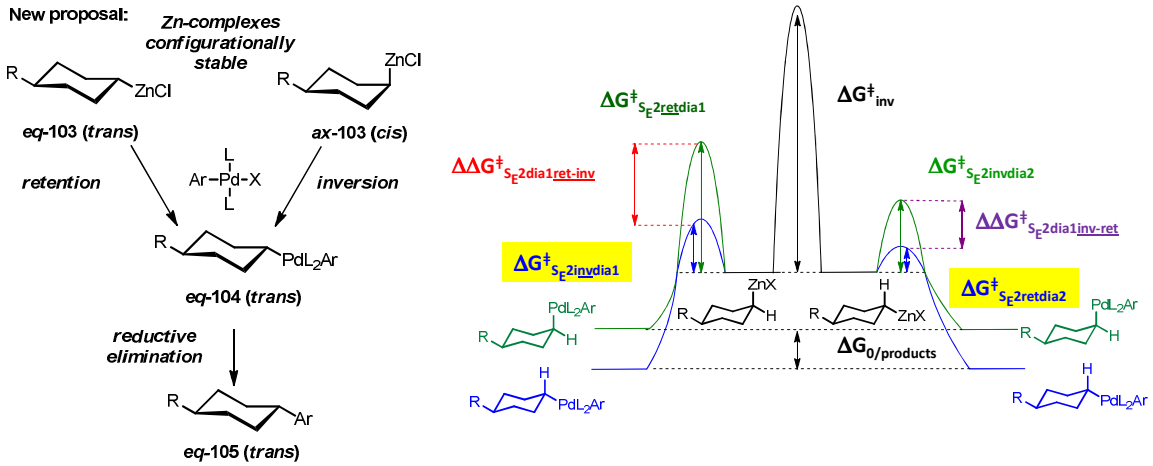
showing distinct behaviour. DFT-calculations demonstrated that the formation of oligomeric cyclohexyllithium structures is the key determinant for the observed stereochemical preference.



Scheme 46: A new practical stereoretentive I-Li exchange reaction for the stereoselective preparation of cyclohexyllithiums. The behaviours of the resulting diastereomeric substituted cyclohexyllithium reagents were studied.

5.2. Novel Insights into the Stereochemical Behaviour of Diastereomeric Cyclohexylzinc Reagents – Stereoconvergence through Distinct Stereochemical Pathways

A novel revised mechanistic view of the stereoconvergent *Negishi*-cross-coupling of substituted cyclohexylzinc reagents has been established through our investigations. The observed high configurational stability of the C-Zn bond excludes a mechanism based on a dynamic kinetic resolution process, since flipping of the C-Zn bond takes place too slowly. Via deuterolysis and protolysis experiments, we were able to show that high stereoselectivities can be achieved in quenching diastereomeric cyclohexylzinc reagents with preference of the all equatorially substituted products, excluding an equilibration on the stage of the cyclohexyl-palladium intermediates as key factor for the stereoconvergence. Moreover, both diastereomers were observed to react with the same observable rate at the NMR time scale in slow addition/protolysis. In combination, these crucial results along with the fact that only one Pd-intermediate could be observed in the cross-coupling[68] show that the equatorial C-Zn bond must react with retention and the axial C-Zn bond with inversion of the stereoconfiguration in the transmetalation step to $ArPdL_nX$ thus leading to stereoconvergence in the reaction (Scheme 47).



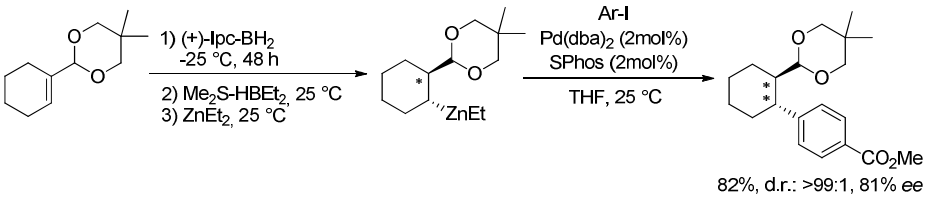
Scheme 47: Substituted diastereomeric cyclohexylzinc complexes ***eq*-103** and ***ax*-103** which differ in the configuration of their C-Zn bond undergo distinct stereochemical pathways in the transmetallation to $ArPdL_nX$ thus leading to overall stereoconvergence in the cross-coupling reaction. The energy diagram sums up the experimental observations. The high energetic barrier between the diastereomeric zinc reagents prevents their equilibration. The fact that reaction pathways for diastereomers do not need to be isoenergetic, as is the case for enantiomers, allows distinct stereochemical reactivities. Thus, the axially configured cyclohexylzinc diastereomer reacts with inversion and the equatorially substituted one with retention of the stereoconfiguration resulting in overall stereoconvergence of the reaction.

To the best of our knowledge, this work represents the first experimental proof that diastereomeric organometallics can undergo distinct stereochemical pathways which result in the stereoselective formation of one diastereomerically defined product. We anticipate that in addition to the dynamic resolution processes which have been well established for configurationally unstable organolithiums, these observations will lead to the further understanding and development of stereoconvergent reactions for configurationally stable alkyl organometallics.

5.3. Diastereo- and Enantioselective Cross-Coupling with Functionalized Cyclohexylzinc Reagents

Cross-couplings of functionalized cyclohexylzinc reagents such as [2-(1,3-dioxolan-2-yl)cyclohexyl]- and [2-(5,5-dimethyl-1,3-dioxan-2-yl)cyclohexyl]zinc reagents (**142**, **143** und **140**, **141**) lead to high diastereoselectivities. *β*-Hydride eliminations which were observed in cross-coupling reactions of the organizinc iodides **142** and **143** could be avoided by decreasing the temperature to -25 °C. Moreover, it was illustrated that cross-coupling of diorganozinc complexes **140** and **141** can be successfully performed even at higher

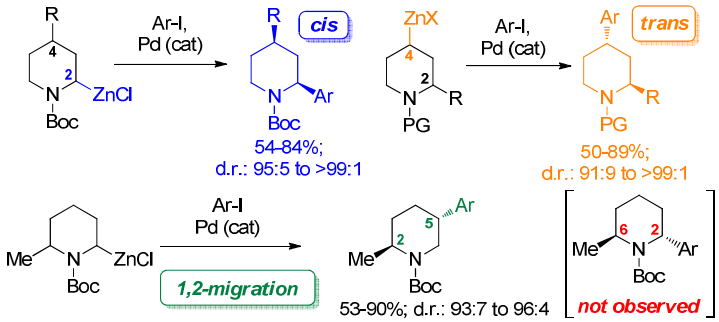
temperatures up to 25 °C without loss in diastereoselectivity. Hereby, *β*-hydride elimination processes did not occur which can be probably explained by the stereochemically pure nature featuring only an equatorial C-Zn bond. Cross-coupling of the chiral organozinc reagents **159** and **160** synthesized *via* enantioselective hydroboration, proceeded diastereoselectively and furnished the respective arylated 1,2-disubstituted cyclohexanes in moderate enantiomeric excess. Cross-coupling of [8-(ethoxymethoxy)decahydronaphthalen-1-yl](ethyl)zinc (**170**) was performed with moderate diastereoselectivity. Since the arylation of **170** proceeds with high stereoselectivity, *β*-hydride elimination processes on the step of the palladium intermediate can be responsible for the observed low diastereoselectivity.



Scheme 48: Enantio- and diastereoselective arylation via a hydroboration/B-Zn-exchange/cross-coupling sequence.

5.4. Highly Diastereoselective Arylations of Substituted Piperidines

A highly diastereoselective methodology for the preparation of various substituted piperidines via *Negishi* cross-couplings with (hetero)aryl iodides was developed. Depending on the position of the C-Zn bond relative to the nitrogen (position 2 vs. position 4), the stereoselectivity of the coupling can be directed either towards the *trans*- or the *cis*-2,4-disubstituted products. DFT-calculations on the relative stabilities of the Zn- and Pd-intermediates were performed to explain the high diastereoselectivities obtained. A novel Pd-1,2-migration further expands this method to the stereoselective preparation of 5-arylated 2,5-disubstituted piperidines.



Scheme 49: Switchable stereoselectivity in the cross-couplings of piperidinylzinc reagents and a novel diastereoselective Pd-1,2-migration.

C. Experimental Section

1. General Considerations

All reactions were carried out with magnetic stirring and, if the reagents were air or moisture sensitive, in flame-dried glassware under argon. Syringes which were used to transfer reagents and solvents were purged with argon prior to use.

1.1. Solvents

Solvents were dried according to standard procedures by distillation over drying agents and stored under argon.

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2.

DMF was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

1,4-Dioxane was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

Et_2O was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

NEP was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

Pyridine was dried over KOH and distilled.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Toluene was predried over $CaCl_2$ and distilled from CaH_2.

Triethylamine was dried over KOH and distilled.

Solvents for column chromatography were distilled prior to use.

1.2. Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid aldehydes and acid chlorides were distilled prior to use.

***i*PrMgCl·LiCl** solution in THF was purchased from Rockwood Lithium (Chemetall).

***i*PrMgCl** solution in THF was purchased from Rockwood Lithium (Chemetall).

PhMgCl solution in THF was purchased from Rockwood Lithium (Chemetall).

***n*BuLi** solution in *n*-hexane was purchased from Rockwood Lithium (Chemetall).

***s*BuLi** solution in cyclohexane was purchased from Rockwood Lithium (Chemetall).

***t*BuLi** solution in *n*-pentane was purchased from Rockwood Lithium (Chemetall).

Content determination of organometallic reagents

The respective organometallic reagents were titrated using either the method reported by *Paquette*[83] or *Knochel*[84] prior to their use.

$ZnCl_2$ solution (1.00 M) was prepared by drying $ZnCl_2$ (100 mmol, 136 g) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling to room temperature, 100 mL dry THF were added and stirring was continued until the salt was dissolved. The reagent was stirred under a nitrogen atmosphere.

$MgCl_2$ solution (0.5 M) was prepared by drying magnesium turnings (30 mmol, 0.73 g) in a *Schlenk*-flask under high vacuum at 140 °C for 15 min. After cooling to room temperature, 60 mL dry THF was filled in. The mixture was vigorously stirred and 1,2-dichloroethane (30 mmol, 2.38 mL) was carefully added dropwise until all magnesium filings had been consumed. The reagent was stirred under a nitrogen atmosphere.

CuCN·2LiCl solution (1.00 m) was prepared by drying LiCl (8.48 g, 200 mmol) and CuCN (8.96 g, 100 mmol) for 5 h at 140 °C under high vacuum. After cooling to room temperature, 100 mL dry THF were added and stirring was continued until the salt was dissolved. The *Schlenk*-tube was wrapped in an aluminium-foil to protect from light. The reagent appears as a slightly greenish solution and has to be stored under argon.

Preparation of a 0.7 M solution of *c*HexMgBr in THF

In a dry and Ar-flushed 250 mL 3-necked flask, equipped with a reflux condenser, a dropping funnel and a magnetic stirring bar, LiCl (2.33 g, 55.0 mmol) was placed and dried over 10 min at 500 °C in high vacuum (1 mbar). After cooling to room temperature Mg turnings (1.34 g, 55.0 mmol) and 1,2-dibromoethane (0.52 g, 0.24 mL, 2.75 mmol) were added. The heterogeneous mixture was vigorously stirred before THF (38.5 mL) was added and then gently heated in order to activate the Mg surface. A solution of cyclohexyl bromide (8.15 g, 6.13 mL, 50.0 mmol) in THF (15 mL) was added dropwise and the resulting reaction mixture was stirred for 45 min at room temperature.

[83] Lin, H.-S. & Paquette, L. A. A convenient method for determining the concentration of Grignard reagents. *Synth. Commun*. **24**, 2503-2506 (1994).
[84] Krasovskiy, A. & Knochel, P. Convenient titration method for organometallic zinc, magnesium, and lanthanide reagents. *Synthesis* **5**, 890-891 (2006).

Preparation of a 7.3 M solution of Et_2BH in SMe_2

In a dry and Ar-flushed 50 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, $BH_3{\cdot}SMe_2$ (3.80 g, 4.74 mL, 50.0 mmol) was placed and neat BEt_3 (9.80 g, 14.5 mL, 100 mmol) was added dropwise. The resulting solution was stirred at room temperature for 48 h. It was stored in a freezer (–28 °C).

Preparation of a 1.0 M solution of (–)-$IpcBH_2$ in THF

In a dry and Ar-flushed 100 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, $[(–)\text{-}IpcBH_2]_2{\cdot}$TMEDA-complex (5.00 g, 12.0 mmol) was dissolved in THF (24 mL) at room temperature and freshly distilled $BF_3{\cdot}Et_2O$-complex (3.40 g, 3.00 mL, 24.0 mmol) was added dropwise. The reaction mixture was stirred for 2 h and then filtrated through a *Schlenk*-frit into an Ar-flushed *Schlenk*-tube. The precipitate was washed with a small amount of THF. The solution was concentrated (0.1 mm Hg, 25 °C, 2 h) and the residue redissolved in THF (24 mL).

1.3. Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from Merck.

Thin layer chromatography was performed using SiO_2 pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under UV light at 254 nm and/or by staining of the TLC plate with one of the solutions given below followed by heating with a heat gun:

- $KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL).
- Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in water (230 mL).

1.4. Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual solvent peak of $CHCl_3$ (δ_H: 7.25, δ_C: 77.0). For the characterization of the observed signal multiplicities the following appreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet) as well as br (broad).

Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an electron energy of 70 eV.

For the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890 / MSD 5973 was used.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. The absorption bands are reported in wavenumbers (cm^{-1}).

Melting points (M.p.) were determined on a BÜCHI B-540 apparatus and are uncorrected.

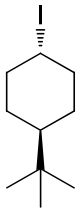
2. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted Cyclohexyllithium Derivatives

2.1. Preparation of Starting Materials

2.1.1. Typical Procedure 1: Iodination of alcohols (TP1)

A 1.0 M solution of I_2 in CH_2Cl_2 was prepared in a flame-dried, Ar-flushed *Schlenk*-flask equipped with a stirring bar and cooled to 0 °C using a *Huber T100* cryostat. PPh_3 (1.2 equiv.) was added portionwise. The resulting suspension was stirred for 1 h, before *N*-methyl-imidazole (NMI; 1.2 equiv.) was added. The reaction mixture became a bright yellow suspension and the respective alcohol was added portionwise. The resulting mixture was stirred for 15 h at 0 °C, then quenched with $NaHSO_3$ sat. solution. The phases were separated and the aqueous phase was extracted with 3 x CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and the solvents evaporated (35 °C, rotavap, 8 mbar, <30 min). Column chromatographic purification (flash silica) was performed. The solvents were evaporated (35 °C, rotavap, 8 mbar, <30 min) and, if necessary, the product was subjected to high vacuum (10^{-3} mbar) at 30 °C in order to remove cyclohexene/elimination byproducts. The neat corresponding cyclohexyl iodides were thus obtained.

***trans*-1-(*tert*-butyl)-4-iodocyclohexane (*trans-(eq)*-78)**



column chromatography: SiO_2; *i*-hexane

yield: 3.0 g (20%), colourless oil

d.r.: 10:90.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.10 (tt, J_1=12.3 Hz, J_2=4.0 Hz, 1 H), 2.48 (d, J=11.9 Hz, 2 H), 2.05–1.90 (m, 2 H), 1.72–1.61 (m, 2 H), 1.17–1.02 (m, 3 H), 0.83 (s, 9 H).

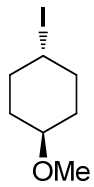
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 46.7, 41.1, 32.6, 30.9, 30.3, 27.4.

MS (70 eV, EI) *m/z* (%): 266 (12) [M^+], 140 (14), 139 (100), 128 (12), 123 (18), 97 (15), 95 (10), 83 (45), 81 (20), 69 (20), 67 (18), 57 (65), 55 (20), 40 (16).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2943 (vs), 2859 (m), 1478 (m), 1469 (m), 1448 (m), 1394 (w), 1366 (m), 1265 (w), 1258 (w), 1249 (w), 1228 (w), 1196 (w), 1188 (w), 1147 (s), 1079 (m), 996 (s), 897 (w), 810 (w), 663 (s).

HRMS (EI) for **$C_{10}H_{19}I$** (266.0531): 266.0518.

***trans*-1-iodo-4-methoxycyclohexane (*trans-(eq)*-83b)**



column chromatography: SiO_2; *i*-hexane

yield: 0.91 g (30%), colourless oil

d.r.: 5:95.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.29–4.23 (m, 1 H), 3.28 (s, 3 H), 3.22 (tt, J_1=8.8 Hz, J_2=3.2 Hz, 1 H), 2.22–2.18 (m, 2 H), 1.92–1.83 (m, 4 H), 1.43–1.35 (m, 2 H).

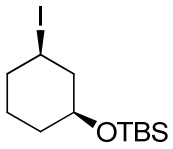
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 76.6, 55.9, 36.4, 31.9, 30.7.

MS (70 eV, EI) *m/z* (%): 240 (6) [M^+], 191 (28), 175 (65), 128 (21), 113 (38), 85 (40), 83 (54), 81 (100), 58 (19), 43 (14).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2942, 2863, 1454, 1369, 1230, 1159, 1102, 1089, 1010, 898, 800, 678.

HRMS (EI) for **$C_7H_{13}IO$** (240.0011): 239.9995.

***tert*-butyl((*cis*-3-iodocyclohexyl)oxy)dimethylsilane (*cis-(eq)*-86b)**



column chromatography: SiO_2; *i*-hexane

yield: 6.75 g (27%), colourless oil

d.r.: 97:3.

^{1}H-NMR (400 MHz, C_6D_6) δ: 4.51–4.35 (m, 1 H), 3.78 (br. s., 1 H), 2.02–1.85 (m, 2 H), 1.73–1.64 (m, 2 H), 1.57–1.47 (m, 1 H), 1.33 (br. s., 3 H), 0.92 (s, 9 H), -0.02 (s, 3 H), -0.01 (s, 3 H).

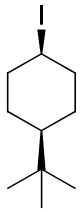
^{13}C-NMR (101 MHz, C_6D_6) δ: 69.5, 47.4, 39.0, 34.1, 28.9, 26.4, 22.9, 18.6, 4.4.

MS (70 eV, EI) *m/z* (%): 340 (8) [M^+], 284 (10), 213 (12), 155 (16), 81 (100), 75 (49), 73 (17).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2929 (m), 2857 (m), 1252 (m), 1240 (m), 1152 (m), 1099 (s), 1068 (m), 1053 (s), 1032 (s), 1006 (m), 902 (m), 871 (m), 852 (m), 834 (vs), 824 (s), 799 (m), 773 (vs), 688 (m).

HRMS (EI) for **$C_{12}H_{25}IOSi$** (340.0719): 340.0714.

***cis*-1-(*tert*-butyl)-4-iodocyclohexane (*cis-(ax)*-78)**



column chromatography: SiO_2; *i*-hexane

yield: 7.5 g (57%), white solid

d.r.: 98:2.

m.p.: 32.8 – 34.9 °C.

^{1}H-NMR (599 MHz, $CDCl_3$) δ: 4.89 (br. s., 1 H), 2.13 (d, J=14.0 Hz, 2 H), 1.68–1.62 (m, 2 H), 1.60–1.47 (m, 4 H), 1.08 (tt, J_1=11.5 Hz, J_2=3.3 Hz, 1 H), 0.90 (s, 9 H).

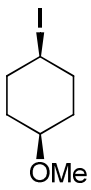
^{13}C-NMR (151 MHz, $CDCl_3$) δ: 47.8, 37.9, 36.9, 32.6, 27.4, 23.3.

MS (70 eV, EI) *m/z* (%): 266 (8) [M^+], 140 (11), 139 (100), 123 (15), 83 (47), 81 (21), 69 (17), 67 (18), 57 (69), 55 (17), 41 (14).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2956 (s), 2939 (vs), 2921 (m), 2885 (m), 2863 (m), 2845 (m), 2832 (m), 1482 (w), 1472 (w), 1444 (w), 1430 (m), 1418 (m), 1390 (w), 1366 (m), 1350 (w), 1308 (m), 1243 (m), 1232 (m), 1186 (s), 1016 (m), 996 (m), 851 (m), 764 (w), 652 (m).

HRMS (EI) for **$C_{10}H_{19}I$** (266.0531): 266.0530.

***cis*-1-iodo-4-methoxycyclohexane (*cis-(ax)*-83b)**



column chromatography: SiO_2; *i*-hexane

yield: 0.64 g (30%), colourless oil

d.r.: 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.42–4.38 (m, 1 H), 3.37–3.31 (m, 1 H), 3.30 (s, 3 H), 2.23–2.14 (m, 2 H), 1.87–1.80 (m, 2 H), 1.79–1.73 (m, 2 H), 1.67–1.61 (m, 2 H).

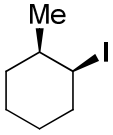
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 75.6, 55.8, 34.9, 31.5, 30.3.

MS (70 eV, EI) *m/z* (%): 240 (6) [M^+], 113 (25), 81 (100), 71 (13), 58 (13), 45 (11), 43 (14), 41 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2939, 2859, 2820, 1446, 1371, 1229, 1163, 1101, 1089, 1001, 933, 898, 806, 675.

HRMS (EI) for **$C_7H_{13}IO$** (240.0011): 240.0003.

***cis*-1-iodo-2-methylcyclohexane (*cis-(ax)*-98)**



column chromatography: SiO_2; *i*-hexane

yield: 4.7 g (48%), colourless oil

d.r.: 98:2.

^{1}H-NMR (300 MHz, C_6D_6) δ: 4.26 (d, *J*=2.5 Hz, 1 H), 2.02–1.92 (m, 1 H), 1.80–1.64 (m, 1 H), 1.45 (dddd, J_1=12.9 Hz, J_2=3.7 Hz, J_3=3.6 Hz, J_4=1.4 Hz, 1 H), 1.37–1.20 (m, 3 H), 1.17–1.08 (m, 1 H), 1.08–0.89 (m, 1 H), 0.80 (d, *J*=6.6 Hz, 3 H), 0.23–0.10 (m, 1 H).

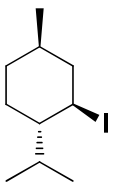
^{13}C-NMR (75 MHz, C_6D_6) δ: 49.7, 38.0, 37.1, 31.2, 25.7, 24.6, 23.3.

MS (70 eV, EI) *m/z* (%): 224 (72) [M^+], 98 (13), 97 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (m), 2925 (vs), 2853 (m), 2834 (m), 1452 (m), 1442 (m), 1377 (w), 1335 (w), 1318 (w), 1290 (w), 1256 (m), 1246 (m), 1211 (m), 1162 (s), 964 (w), 955 (m), 872 (w), 815 (w), 760 (w).

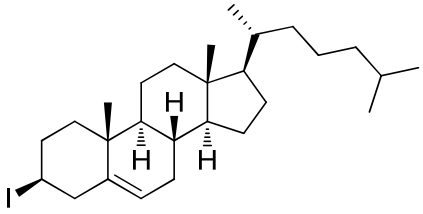
HRMS (EI) for **$C_7H_{13}I$** (224.0062): 224.0053.

(1*R*,2*R*,4*R*)-2-iodo-1-isopropyl-4-methylcyclohexane (*men-(eq)*-89)



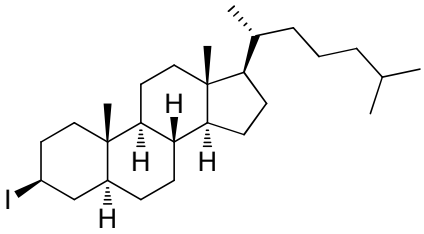
Lepore, S. D., Mondal, D., Li, S. Y. & Bhunia, A. K., *Angew. Chem. Int. Ed.* **47**, 7511-7514 (2008).

***β-cholesteryl iodide* (*β-(eq)*-92)**



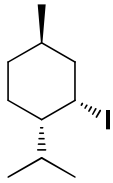
Sun, Q., Cai, S. & Peterson, B. R., *Org. Lett.* **11**, 567-570 (2009).

***β-cholestanyl iodide* (*β-(eq)*-95)**



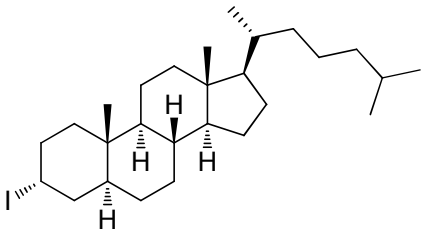
Bayless, A. V. & Zimmer, H., *Tetrahedron Lett.* **35**, 3811-3812 (1968).

(1*R*,2*S*,4*R*)-2-iodo-1-isopropyl-4-methylcyclohexane (*neomen-(ax)*-89)



Lange, G. L. & Gottardo, C. *Synth. Commun.* **20**, 1473–1479 (1990).

***α-cholestanyl iodide* (*α-(ax)*-95)**



Lange, G. L. & Gottardo, C. *Synth. Commun.* **20**, 1473–1479 (1990).

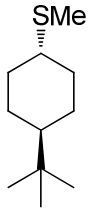
2.2. I-Li Exchange and Subsequent Quenching with Electrophiles

2.2.1. Typical Procedure 2: I-Li exchange and subsequent quenching with electrophiles (TP2)

(Compounds of **Scheme 23**, **Table 1**, **Table 2**, **Table 3** and **Scheme 24**)

A solution of *n*-hexane/ether (3:2; 5.5 mL) was placed into a flame-dried and Ar-flushed Schlenk-tube equipped with a stirring bar and cooled to -100 °C using a *Huber T100* cryostat. A *t*BuLi solution (2.2 equiv.; 1.3 M in *n*-hexane; 0.84 mL; 1.1 mmol) was added via syringe. After 5 min, a 1.0 M solution (0.5 M for the cholesteryl and cholestanyl derivatives **92** and **95**) of the respective cyclohexyl iodide (1.0 equiv.; 0.5 mmol) in *n*-hexane/ether (3:2) was added. The reaction was directly quenched after 4-5 s with the corresponding electrophile (4 equiv.; 0.18 mL; 2 mmol; solid Ph_3SnCl was added as a 1 M solution in Et_2O). The reaction mixture was stirred for 5 min at -100 °C before NH_4Cl sat. aq solution (2 mL) was added. After warming to room temperature the phases were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvents were evaporated. Column chromatographic purification of the crude material (flash silica) provided the respective products.

(*trans*-4-(*tert*-butyl)cyclohexyl)(methyl)sulfane (*trans-(eq)*-82a) (Scheme 28)



column chromatography: SiO_2; *i*-hexane

yield: 84 mg (90%), colourless oil

d.r.: 9:91.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.43 (tt, J_1=12.0 Hz, J_2=3.6 Hz, 1 H), 2.09 (s, 3 H), 2.06 (br. s., 1 H), 1.84 (d, J=10.0 Hz, 2 H), 1.36–1.15 (m, 3 H), 1.13–0.96 (m, 3 H), 0.85 (s, 9 H).

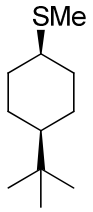
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 47.5, 44.9, 33.7, 32.4, 27.6, 27.5, 13.1.

MS (70 eV, EI) *m/z* (%): 186 (100) [M^+], 175 (89), 138 (49), 129 (55), 123 (48), 95 (54), 83 (55), 82 (40), 81 (87), 69 (32), 67 (31), 57 (92), 55 (35), 41 (32).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2936 (vs), 2856 (s), 1478 (m), 1467 (m), 1448 (m), 1394 (w), 1365 (s), 1275 (w), 1235 (w), 1230 (w), 1211 (w), 1174 (w), 1038 (w), 1013 (m), 1006 (m), 970 (w), 954 (w), 897 (w).

HRMS (EI) for **$C_{11}H_{22}S$** (186.1442): 186.1432.

(*cis*-4-(*tert*-butyl)cyclohexyl)(methyl)sulfane (*cis*-*(ax)*-82a) (Scheme 23)



column chromatography: SiO_2; *i*-hexane

yield: 68 mg (73%), colourless oil

d.r.: 90:10.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.03 (br. s., 1 H), 2.06 (s, 3 H), 1.95 (d, J=14.1 Hz, 2 H), 1.66 (tt, J_1=13.4 Hz, J_2=3.7 Hz, 2 H), 1.59–1.49 (m, 2 H), 1.49–1.34 (m, 2 H), 1.07–0.96 (m, 1 H), 0.86 (s, 9 H).

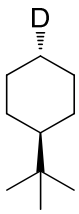
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 48.4, 44.3, 32.6, 31.1, 27.5, 21.9, 14.8.

MS (70 eV, EI) *m/z* (%): 186 (8) [M^+], 175 (28), 147 (25), 83 (10), 57 (22).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2938 (vs), 2930 (vs), 2864 (m), 2846 (m), 1478 (m), 1467 (m), 1440 (m), 1393 (w), 1365 (s), 1312 (m), 1263 (m), 1237 (w), 1227 (w), 1214 (m), 1024 (w), 865 (w), 770 (w).

HRMS (EI) for **$C_{11}H_{22}S$** (186.1442): 186.1443.

***trans*-*tert*-butyl(4-$^2H_1$)cyclohexane (*trans*-*(eq)*-82d) (Table 1)**

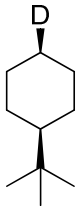


yield: (85%)

d.r.: 4:96.

^{2}H-NMR (61 MHz, THF) δ: 1.53 (s, 1 D).

***cis-tert*-butyl(4-$^{2}H_1$)cyclohexane (*cis-(ax)*-82d) (Table 1)**

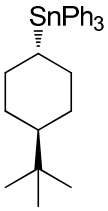


yield: 75% (GC)

d.r.: 92:8.

^{2}H NMR (61 MHz, THF) δ: 0.99 (s, 1 D).

(*trans*-4-(*tert*-butyl)cyclohexyl)triphenylstannane (*trans-(eq)*-82f) (Table 1)



column chromatography: SiO_2; *i*-hexane/Et_2O 40:1

yield: 127 mg (52 %), white solid

d.r.:8:92.

m.p.: 99.1 – 101.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.65–7.55 (m, 5 H), 7.51–7.36 (m, 10 H), 2.22 (dd, J_1=12.0 Hz, J_2=1.2 Hz, 2 H), 2.03–1.80 (m, 3 H), 1.79–1.63 (m, 2 H), 1.12–1.00 (m, 3 H), 0.84 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 138.8, 137.4, 128.7, 128.4, 48.2, 32.5, 32.2, 29.9, 28.5, 27.4.

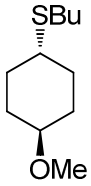
^{119}Sn-NMR (149 MHz, $CDCl_3$) δ: 116.34 (major) -107.77 (minor).

MS (70 eV, EI) *m/z* (%): 490 (3) [M^+], 355 (17), 353 (16), 352 (20), 351 (100), 350 (39), 349 (76), 348 (33), 347 (45), 196 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3061 (w), 2956 (m), 2917 (m), 2849 (m), 1480 (w), 1467 (w), 1444 (w), 1427 (m), 1390 (w), 1362 (w), 1300 (w), 1231 (w), 1190 (w), 1148 (w), 1073 (m), 1060 (w), 1023 (w), 997 (w), 874 (w), 724 (s), 697 (vs), 666 (w), 657 (w).

HRMS (EI) for **$C_{28}H_{34}Sn$** (490.1682): 490.1690.

butyl(*trans*-4-methoxycyclohexyl)sulfane (*trans-(eq)*-85b) (Table 2)



column chromatography: SiO_2; *i*-hexane/Et_2O 25:1

yield: 84 mg (83%), colourless oil

d.r.: <1:99.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.33–3.28 (m, 1 H), 3.27 (s, 3 H), 2.69 (quint, *J*=6.4 Hz, 1 H), 2.49 (t, *J*=7.5 Hz, 2 H), 1.90–1.81 (m, 2 H), 1.72–1.66 (m, 4 H), 1.55–1.48 (m, 4 H), 1.41–1.33 (m, 2 H), 0.88 (t, *J*=7.2 Hz, 3 H).

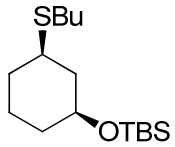
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 75.7, 55.7, 42.7, 32.3, 30.3, 29.1, 28.6, 22.3, 13.9.

MS (70 eV, EI) *m/z* (%): 202 (64) [M^+], 170 (15), 116 (23), 113 (10), 81 (70), 80 (100), 79 (14), 71 (11), 58 (14), 43 (12), 41 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2931, 2856, 1451, 1374, 1187, 1145, 1099, 933, 746.

HRMS (EI) for **$C_{11}H_{22}OS$** (202.1391): 202.1392.

***tert*-butyl((*cis*-3-(butylthio)cyclohexyl)oxy)dimethylsilane (*cis-(eq)*-88b) (Table 2)**



column chromatography: SiO_2; *i*-hexane/Et_2O 40:1

yield: 95 mg (63%), colourless oil

d.r.: 2:98.

^{1}H-NMR (400 MHz, C_6D_6) δ: 3.55–3.43 (m, 1 H), 2.37–2.31 (m, 1 H) 2.47–2.37 (m, 3 H), 1.81 (t, *J*=15.4 Hz, 2 H), 1.56–1.45 (m, 4 H), 1.30 (dq, J_1=15.0 Hz, J_2=7.5 Hz, 3 H), 1.17–1.01 (m, 2 H), 0.98 (s, 9 H), 0.81 (t, *J*=7.4 Hz, 3 H), 0.06 (s, 6 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 71.7, 44.3, 41.9, 36.3, 33.7, 32.8, 30.3, 26.4, 24.6, 22.7, 18.6, 14.2, 4.0.

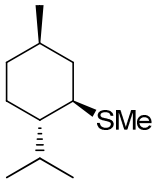
^{29}Si-NMR (80 MHz, C_6D_6) δ: 16.4.

MS (70 eV, EI) *m/z* (%): 302 (1) [M^+], 246 (16), 245 (100), 155 (24), 147 (15), 81 (1), 75 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2857 (m), 1462 (w), 1372 (w), 1255 (m), 1250 (m), 1124 (m), 1086 (s), 1006 (w), 976 (m), 878 (m), 860 (m), 846 (s), 834 (vs), 803 (m), 773 (vs), 666 (m).

HRMS (EI) for **$C_{16}H_{34}OSSi$** (302.2100): 302.2094.

((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)(methyl)sulfane (*men-(eq)*-91a) (Table 2)



column chromatography: SiO_2; *i*-hexane

yield: 50 mg (54%), colourless oil

d.r.: 13:87.

^{1}H-NMR (400 MHz, C_6D_6) δ: 2.68–2.53 (m, 1 H), 2.25 (td, J_1=11.2 Hz, J_2=3.71 Hz, 1 H), 2.09–1.98 (m, 1 H), 1.80 (s, 3 H), 1.62–1.52 (m, 2 H), 1.23–1.03 (m, 3 H), 0.96–0.86 (m, 4 H), 0.84 (d, J=6.3 Hz, 3 H), 0.80 (d, J=6.9 Hz, 3 H), 0.77–0.69 (m, 1 H).

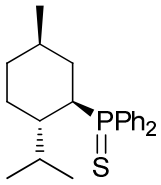
^{13}C-NMR (101 MHz, C_6D_6) δ: 48.0, 46.9, 43.6, 35.4, 33.8, 27.9, 25.3, 22.8, 21.9, 15.9, 12.3.

MS (70 eV, EI) *m/z* (%): 186 (86) [M^+], 138 (93), 123 (51), 97 (35), 95 (100), 85 (33), 83 (69), 82 (32), 81 (57), 71 (31), 69 (50), 57 (51), 55 (39).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (vs), 2918 (vs), 2869 (m), 2848 (m), 1454 (m), 1446 (m), 1385 (w), 1368 (w), 1300 (w), 1198 (w), 955 (w), 934 (w).

HRMS (EI) for **$C_{11}H_{22}S$** (186.1442): 186.1440.

((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)diphenylphosphine sulfide (*men-(eq)*-91b) (Table 2)



column chromatography: SiO_2; *i*-hexane/Et_2O 30:1

yield: 105 mg (59 %), white solid

d.r.: 10:90.

m.p.: 163.0 – 166.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.16–8.06 (m, 2 H), 8.06–7.95 (m, 2 H), 7.05–6.93 (m, 6 H), 2.63–2.55 (m, 1 H), 2.29–2.20 (m, 1 H), 1.99 (quin, J=6.7 Hz, 1 H), 1.66 (ddd, J_1=13.0 Hz, J_2=6.2 Hz, J_3=3.2 Hz, 1 H), 1.57 (d, J=11.9 Hz, 1 H), 1.50–1.36 (m, 2 H), 1.33–1.23 (m, 1 H),

1.05 (qd, J_1=12.8 Hz, J_2=3.1 Hz, 1 H), 0.87 (d, J=6.6 Hz, 3 H), 0.85–0.75 (m, 1 H), 0.64 (d, J=6.4 Hz, 3 H), 0.39 (d, J=6.8 Hz, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 135.5 (d, J=72.8 Hz), 134.0 (d, J=76.3 Hz), 131.5 (d, J=9.0 Hz), 131.0 (d, J=9.6 Hz), 130.5 (d, J=3.0 Hz), 130.4 (d, J=2.9 Hz), 128.2 (d, J=9.8 Hz), 128.0 (d, J=9.5 Hz), 44.1 (d, J=1.7 Hz), 39.5 (d, J=53.7 Hz), 35.7 (d, J=1.1 Hz), 34.4 (d, J=1.7 Hz), 33.3 (d, J=14.2 Hz), 27.5 (d, J=4.1 Hz), 24.8 (d, J=13.1 Hz), 22.3 (d, J=0.7 Hz), 21.5, 15.8.

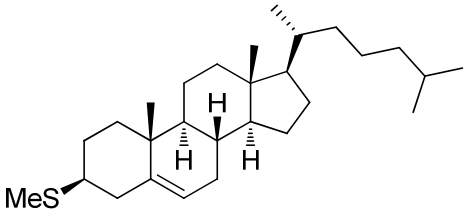
^{31}P-NMR (162 MHz, C_6D_6) δ: 49.5, 43.6.

MS (70 eV, EI) *m/z* (%): 356 (8) [M^+], 219 (26), 218 (100), 185 (11), 183 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2961 (m), 2953 (m), 2942 (w), 2921 (m), 2869 (w), 2844 (w), 1479 (w), 1454 (w), 1436 (m), 1308 (w), 1092 (s), 1068 (w), 1026 (w), 997 (w), 855 (w), 760 (m), 744 (s), 732 (m), 717 (m), 704 (s), 697 (vs), 688 (vs), 660 (s).

HRMS (EI) for **$C_{22}H_{29}PS$** (356.1728): 356.1727.

(*β*-cholesteryl)(methyl)sulfane (*β-(eq)*-94a) (Table 2)



column chromatography: SiO_2; *i*-hexane/CH_2Cl_2 1:1

yield: 147 mg (71%), white solid

d.r.: 1:99.

m.p.: 127.8 – 129.6 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 5.34 (d, J=4.8 Hz, 1 H), 2.50–2.35 (m, 3 H), 2.04 (dt, J_1=12.5 Hz, J_2=3.2 Hz, 1 H), 1.99–1.91 (m, 1 H), 1.91–1.81 (m, 5 H), 1.75 (dt, J_1=13.0 Hz, J_2=3.2 Hz, 1 H), 1.61–1.51 (m, 4 H), 1.47–1.37 (m, 6 H), 1.31–1.05 (m, 8 H), 1.03 (d, J=6.6 Hz, 3 H), 0.99–0.92 (m, 12 H), 0.68 (s, 3 H).

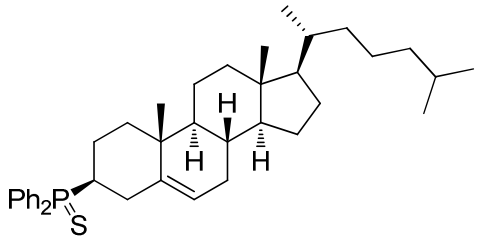
^{13}C-NMR (101 MHz, C_6D_6) δ: 142.4, 121.4, 57.4, 57.0, 51.1, 46.6, 43.0, 40.6, 40.5, 40.3, 37.5, 37.0, 36.6, 32.6, 32.5, 30.1, 29.0, 28.8, 25.0, 24.7, 23.4, 23.1, 21.7, 19.8, 19.4, 13.5, 12.5.

MS (70 eV, EI) *m/z* (%): 416 (28) [M^+], 401 (11), 370 (11), 368 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952 (s), 2928 (vs), 2911 (vs), 2899 (s), 2870 (s), 2852 (s), 1463 (s), 1444 (m), 1431 (m), 1381 (m), 1374 (m), 1366 (m), 960 (m), 825 (m), 800 (m).

HRMS (EI) for **$C_{28}H_{48}S$** (416.3477): 416.3473.

(*β*-cholesteryl)diphenylphosphine sulphide (*β-(eq)*-94b) (Table 2)



column chromatography: SiO_2; *i*-hexane/Et_2O 30:1

yield: 236 mg (80%), white solid

d.r.: 6:94.

m.p.: 184.3 – 186.1 °C.

^{1}H-NMR (400 MHz, C_6D_6) *δ*: 8.01–7.94 (m, 4 H), 7.07–7.02 (m, 6 H), 5.20–5.14 (m, 1 H), 3.12–3.00 (m, 1 H), 2.62–2.53 (m, 1 H), 2.28–2.15 (m, 1 H), 1.99 (d, *J*=12.5 Hz, 2 H), 1.92–1.72 (m, 3 H), 1.58–1.48 (m, 3 H), 1.47–1.33 (m, 8 H), 1.32–1.16 (m, 5 H), 1.16–1.03 (m, 5 H), 1.02–1.00 (m, 6 H), 0.92 (d, *J*=6.6 Hz, 6 H), 0.63 (s, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) *δ*: 141.4 (d, *J*=14.2 Hz), 132.7 (d, *J*=76.1 Hz), 132.5 (d, *J*=76.1 Hz), 131.6 (d, *J*=9.4 Hz), 131.5 (d, *J*=9.4 Hz), 130.9 (d, *J*=3.0 Hz), 130.8 (d, *J*=2.9 Hz), 128.4 (d, *J*=11.5 Hz), 128.3 (d, *J*=11.5 Hz), 121.0, 56.9, 56.3, 50.9 (d, *J*=1.4 Hz), 42.3, 40.0, 39.7, 39.3 (d, *J*=14.6 Hz), 39.0 (d, *J*=55.7 Hz), 37.2 (d, *J*=1.4 Hz), 36.4, 35.9, 32.2 (d, *J*=0.4 Hz), 31.8, 31.5, 28.4, 28.2, 24.3, 24.1, 22.8, 22.5, 21.6 (d, *J*=1.3 Hz), 21.0, 19.2, 18.8, 11.8.

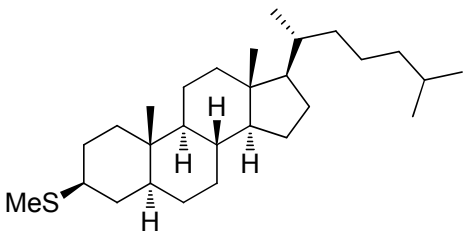
^{31}P-NMR (162 MHz, C_6D_6) *δ*: 49.0.

MS (70 eV, EI) *m/z* (%): 586 (12) [M^+], 369 (16), 368 (27), 220 (15), 219 (73), 218 (100), 186 (16), 185 (17), 183 (17), 140 (10), 108 (11.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2948 (m), 2930 (s), 2888 (m), 2866 (m), 2847 (m), 1463 (m), 1436 (s), 1375 (w), 1101 (s), 827 (w), 778 (m), 751 (m), 742 (m), 732 (m), 709 (vs), 691 (vs).

HRMS (EI) for **$C_{39}H_{55}PS$** (586.3762): 586.3752.

(*β*-cholestanyl)(methyl)sulfane (*β-(eq)*-97) (Table 2)



column chromatography: SiO_2; *i*-hexane/CH_2Cl_2 20:1

yield: 153 mg (74%), white solid

d.r.: 2:98.

m.p.: 79.4 – 81.5 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 2.45–2.37 (m, 1 H), 2.04–1.98 (m, 1 H), 1.91 (s, 3 H), 1.89–1.80 (m, 2 H), 1.68–1.48 (m, 6 H), 1.48–1.28 (m, 6 H), 1.27–1.07 (m, 10 H), 1.03 (d, *J*=6.4 Hz, 3 H), 0.94 (d, *J*=6.6 Hz, 6 H), 0.90–0.77 (m, 2 H), 0.69 (d, *J*=11.4 Hz, 6 H), 0.56 (td, J_1=11.2 Hz, J_2=4.0 Hz, 1 H).

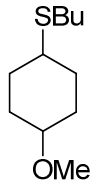
^{13}C-NMR (101 MHz, C_6D_6) δ: 57.2, 57.1, 55.1, 47.5, 45.5, 43.3, 40.8, 40.3, 39.5, 37.0, 36.6, 36.4, 36.3, 36.1, 32.8, 29.8, 29.4, 29.0, 28.8, 24.9, 24.7, 23.4, 23.1, 21.8, 19.4, 13.4, 12.7.

MS (70 eV, EI) *m/z* (%): 418 (100) [M^+], 404 (11), 372 (10), 371 (11), 278 (10), 264 (11), 263 (18), 215 (10), 107 (14), 95 (15), 93 (11), 81 (14), 69 (10), 57 (14), 55 (14), 43 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (s), 2928 (vs), 2863 (s), 2850 (s), 2360 (w), 1739 (m), 1467 (s), 1458 (s), 1443 (m), 1424 (w), 1383 (m), 1379 (m), 1365 (m), 1350 (w), 1232 (w), 1216 (m), 1163 (w), 1155 (w), 961 (w), 954 (w).

HRMS (EI) for **$C_{28}H_{50}S$** (418.3633): 418.3626.

butyl (4-methoxycyclohexyl)sulfane (85b) (Table 3)



column chromatography: SiO_2; *i*-hexane/Et_2O 25:1

yield: 68 mg (67%), colourless oil

d.r.: 52:48.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.30 (s, 3 H), 3.16–3.07 (m, 1 H), 2.60–2.55 (m, 1 H), 2.50 (t, *J*=7.5 Hz, 2 H), 2.07–2.01 (m, 4 H), 1.58–1.48 (m, 2 H), 1.41–1.33 (m, 2 H), 1.32–1.21 (m, 4 H), 0.88 (t, *J*=7.2 Hz, 3 H).

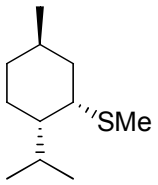
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 78.6, 55.9, 42.6, 32.3, 31.6, 30.4, 22.3, 13.9.

MS (70 eV, EI) *m/z* (%): 202 (90) [M^+], 170 (20), 145 (23), 114 (28), 113 (48), 112 (100), 111 (28), 97 (27), 81 (65), 79 (17), 41 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2931, 2858, 1451, 1374, 1187, 1099, 1024, 933, 746.

HRMS (EI) for **$C_{11}H_{22}OS$** (202.1391): 202.1386.

((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)(methyl)sulfane (*neomen-(ax)*-91a) (Table 3)



column chromatography: SiO_2; *i*-hexane

yield: 21 mg (23%), colourless oil

d.r.: 93:7.

^{1}H-NMR (400 MHz, C_6D_6) δ: 2.86 (d, *J*=1.9 Hz, 1 H), 2.18–2.03 (m, 1 H), 1.93–1.86 (m, 1 H), 1.86–1.81 (m, 1 H), 1.80 (s, 3 H), 1.71–1.62 (m, 2 H), 1.38–1.27 (m, 2 H), 1.05–1.00 (m, 1 H), 0.98 (d, *J*=6.3 Hz, 3 H), 0.90 (d, *J*=6.6 Hz, 3 H), 0.89 (d, *J*=6.6 Hz, 3 H), 0.87–0.74 (m, 2 H).

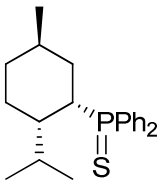
^{13}C-NMR (101 MHz, C_6D_6) δ: 49.6, 49.2, 40.4, 36.1, 30.8, 27.0, 26.8, 22.9, 21.7, 21.3, 15.4.

MS (70 eV, EI) *m/z* (%): 186 (52) [M^+], 139 (26), 138 (73), 123 (27), 101 (16), 97 (32), 96 (22), 95 (100), 94 (10), 83 (69), 82 (21), 81 (50), 79 (11), 69 (38), 68 (12), 67 (27), 61 (10), 57 (37), 55 (53), 53 (14), 43 (24), 41 (46), 39 (12), 29 (11), 27 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2946 (s), 2913 (vs), 2868 (m), 2840 (m), 2360 (w), 1474 (m), 1455 (m), 1444 (m), 1383 (w), 1366 (w), 1297 (w), 1281 (w), 1264 (w), 1241 (w), 863 (w), 859 (w).

HRMS (EI) for **$C_{11}H_{22}S$** (186.1442): 186.1437.

((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)diphenylphosphine sulfide (*neomen-(ax)*-91b) (Table 3)



column chromatography: SiO_2; *i*-hexane/Et_2O 30:1

yield: 50 mg (28%), white solid

d.r.: 91:9.

m.p.: 139.3 – 141.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.18–8.11 (m, 2 H), 8.11–8.05 (m, 2 H), 7.06–6.96 (m, 6 H), 3.17–3.09 (m, 1 H), 3.09–2.96 (m, 1 H), 2.68–2.52 (m, 1 H), 2.09 (sxt, *J*=6.6 Hz, 1 H), 2.02–1.87 (m, 2 H), 1.66–1.42 (m, 2 H), 1.25–1.07 (m, 1 H), 0.97–0.89 (m, 1 H), 0.87 (d, *J*=6.8 Hz, 3 H), 0.67 (d, *J*=6.6 Hz, 3 H), 0.58 (d, *J*=6.4 Hz, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 134.8 (d, *J*=72.9 Hz), 134.7 (d, *J*=75.1 Hz), 131.9 (d, *J*=9.4 Hz), 131.6 (d, *J*=9.0 Hz), 130.5 (d, *J*=3.0 Hz), 130.4 (d, *J*=2.9 Hz), 128.0 (d, *J*=11.3 Hz), 127.9 (d, *J*=11.4 Hz), 48.5 (br), 37.3 (br), 36.8 (d, *J*=52.1 Hz), 34.8 (br), 29.1 (d, *J*=3.4 Hz), 27.0 (d, *J*=3.7 Hz), 23.4 (d, *J*=2.9 Hz), 23.2, 21.9 (s, br), 20.9.

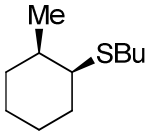
^{31}P-NMR (162 MHz, C_6D_6) δ: 49.5, 43.5.

MS (70 eV, EI) *m/z* (%): 356 (6) [M^+], 219 (25), 218 (100), 183 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950 (w), 2943 (m), 2936 (m), 2916 (w), 2894 (w), 2842 (w), 1476 (w), 1454 (w), 1438 (m), 1367 (w), 1090 (s), 998 (w), 756 (m), 743 (m), 716 (s), 700 (vs), 690 (vs), 680 (s).

HRMS (EI) for **$C_{22}H_{29}PS$** (356.1728): 356.1722.

butyl (*cis*-2-methylcyclohexyl)sulfane (*cis-(ax)*-100) (Table 3)



column chromatography: SiO_2; *i*-hexane

yield: 32 mg (34%), colourless oil

d.r.: 88:12.

^{1}H-NMR (400 MHz, C_6D_6) δ: 2.71–2.65 (m, 1 H), 2.35 (t, *J*=7.4 Hz, 2 H), 1.83–1.69 (m, 3 H), 1.59–1.42 (m, 5 H), 1.36–1.27 (m, 4 H), 1.27–1.14 (m, 1 H), 1.08 (d, *J*=6.8 Hz, 3 H), 0.81 (t, *J*=7.4 Hz, 3 H).

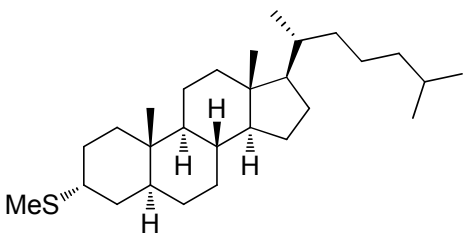
^{13}C-NMR (101 MHz, C_6D_6) δ: 50.6, 36.0, 32.9, 32.4, 32.1, 31.8, 24.8, 23.6, 22.7, 18.6, 14.2.

MS (70 eV, EI) *m/z* (%): 186 (9) [M^+], 146 (10), 145 (100), 103 (19), 97 (20), 96 (16), 87 (13), 81 (12), 61 (24), 57 (12), 55 (41), 41 (16), 29 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957 (s), 2927 (vs), 2870 (m), 2854 (m), 1739 (m), 1454 (m), 1445 (m), 1377 (m), 1366 (w), 1353 (w), 1228 (w), 1217 (m).

HRMS (EI) for **$C_{11}H_{22}S$** (186.1442):186.1440.

(α-cholestanyl)(methyl)sulfane (*α-(ax)*-97) (Table 3)



column chromatography: SiO_2; *i*-hexane

yield: 38 mg (18%), colourless oil

d.r.: 77:23.

^{1}H-NMR (400 MHz, C_6D_6) δ: 2.85 (br. s., 1 H), 1.99 (dt, J_1=12.3 Hz, J_2=3.1 Hz, 1 H), 1.89–1.83 (m, 1 H), 1.83 (s, 3 H), 1.81–1.72 (m, 1 H), 1.72–1.68 (m, 1 H), 1.66–1.49 (m, 7 H), 1.49–1.36 (m, 6 H), 1.29–1.15 (m, 9 H), 1.13–1.05 (m, 4 H), 1.01 (d, J=6.4 Hz, 3 H), 0.92 (d, J=6.4 Hz, 6 H), 0.75 (s, 3 H), 0.70–0.66 (m, 4 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 57.1, 57.0, 54.7, 47.5, 45.5, 43.3, 41.2, 40.7, 40.3, 37.0, 36.7, 36.2, 34.1, 33.9, 32.6, 29.4, 29.0, 28.8, 27.0, 24.9, 24.8, 23.4, 23.2, 21.6, 19.4, 15.4, 12.8, 12.4.

MS (70 eV, EI) *m/z* (%): 418 (51) [M^+], 371 (38), 370 (100), 355 (23), 263 (11), 257 (12), 217 (13), 216 (11), 215 (20), 109 (11), 107 (13), 95 (15), 81 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (vs), 2868 (s), 2851 (s), 1467 (m), 1462 (m), 1452 (m), 1442 (m), 1434 (m), 1379 (m), 1366 (m), 1278 (w), 1258 (w), 1167 (w), 968 (w), 952 (m).

HRMS (EI) for **$C_{28}H_{50}S$** (418.3633): 418.3632.

3. Novel Insights into the Stereochemical Behaviour of Diastereomeric Cyclohexylzinc Reagents – Stereoconvergence through Distinct Stereochemical Pathways

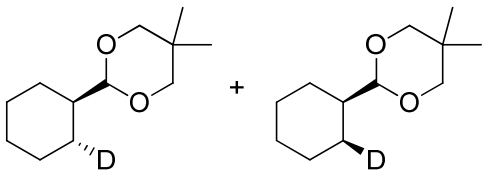
3.1. Deuterolysis and Protolysis Experiments

3.1.1. Typical Procedure 3: Deuterolysis of organozinc reagents (TP 3)

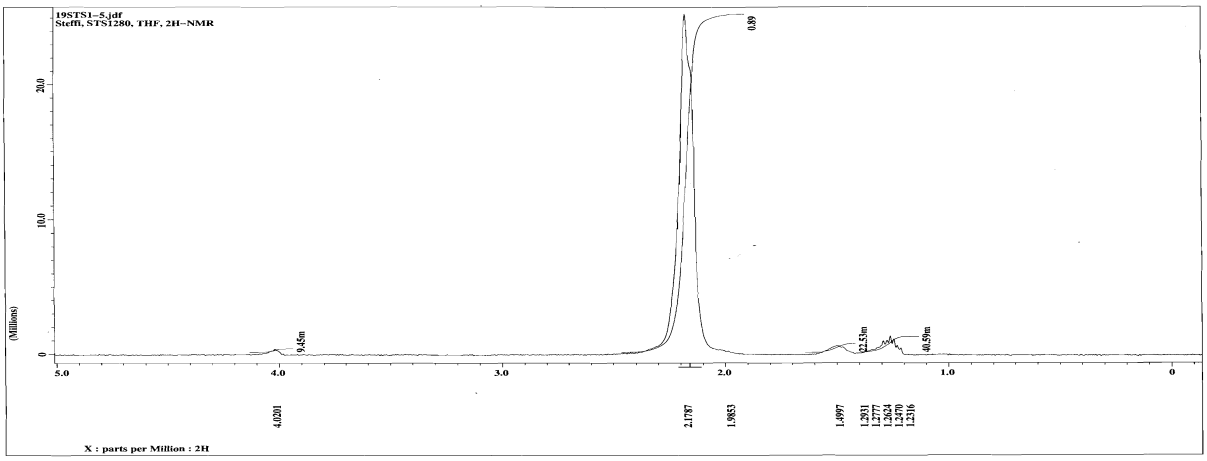
(Compounds of **Scheme 31** and **Table 5**)

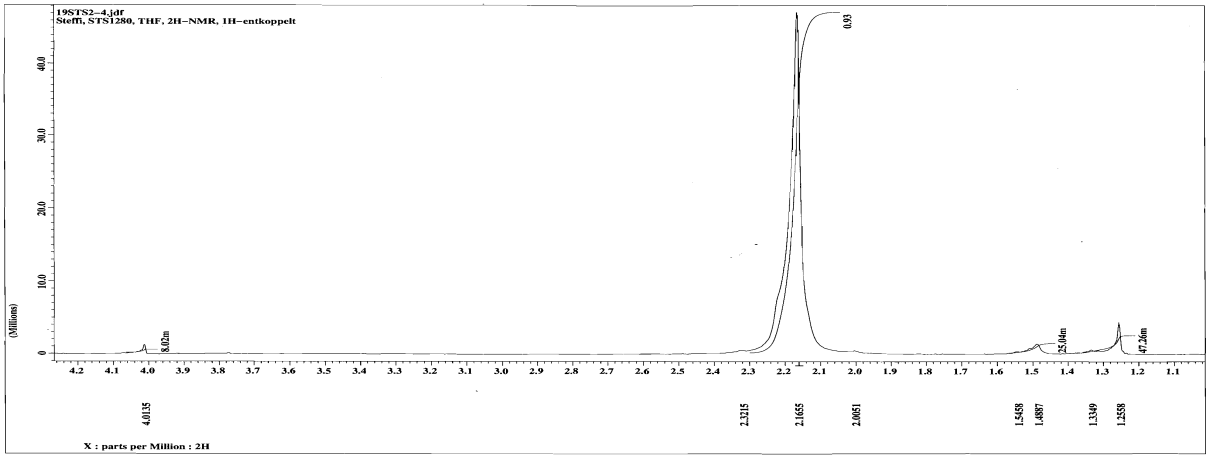
An *in vacuo* dried, Ar-flushed 10 mL *Schlenk*- flask, equipped with a magnetic stirring bar was charged with the respective cyclohexylzinc compound (0.25 mmol, 1.0 equiv.). The flask was then cooled to the corresponding temperature, stirred for 10 min at that temperature before d-TFA (10 equiv.) or MeOD (10 equiv.) were added neat. After 20 min, the reaction was quenched with NH_4Cl sat. solution (2 mL). It was neutralized with $NaHCO_3$ sat. solution. Phases were separated followed by extracting the aqueous phase with 1 mL Et_2O (2 x). The org. phases were combined, dried over Na_2SO_4. The solution was concentrated at the rotary evaporator (careful! Products are volatile!) to 0.6 mL. These were transferred into an NMR tube and analyzed.

2-[*trans*-(2-$^2H_1$)cyclohexyl]-5,5-dimethyl-1,3-dioxane (*trans-(eq)*-114)
&
2-[*cis*-(2-$^2H_1$)cyclohexyl]-5,5-dimethyl-1,3-dioxane (*cis*-(*eq*)-114)



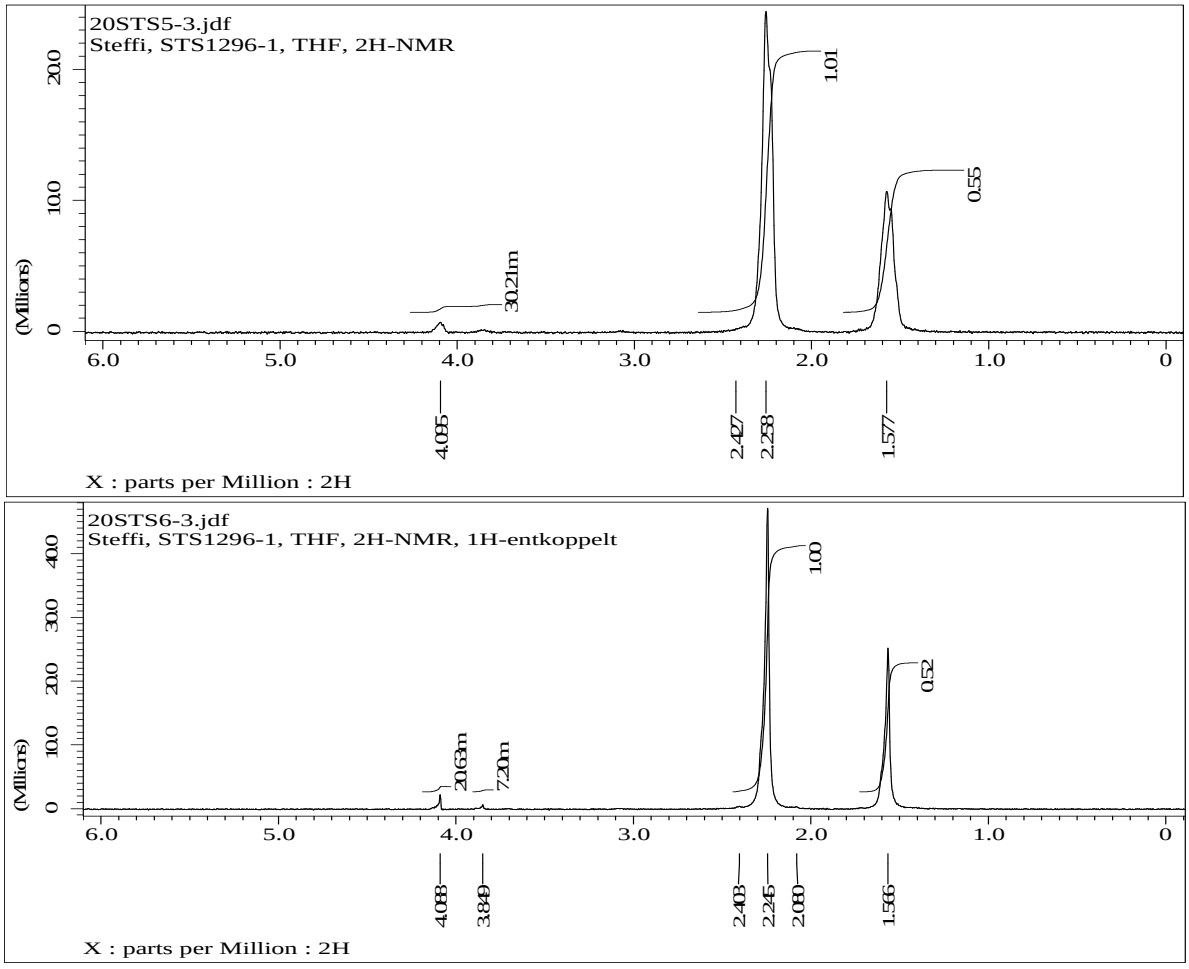
from ***trans-(eq)*-107** (deuterolysis at rt with d-TFA):





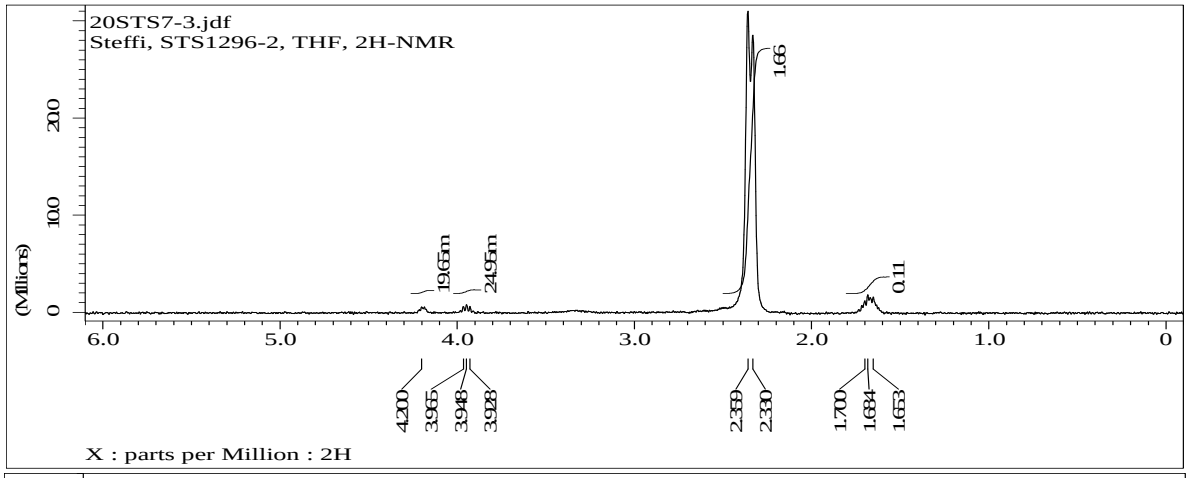
d.r.: 98:2.
^{2}H-NMR (61 MHz, THF) δ: 2.18 (s, 1 D) (major), 1.50 (s, 1 D) (minor).

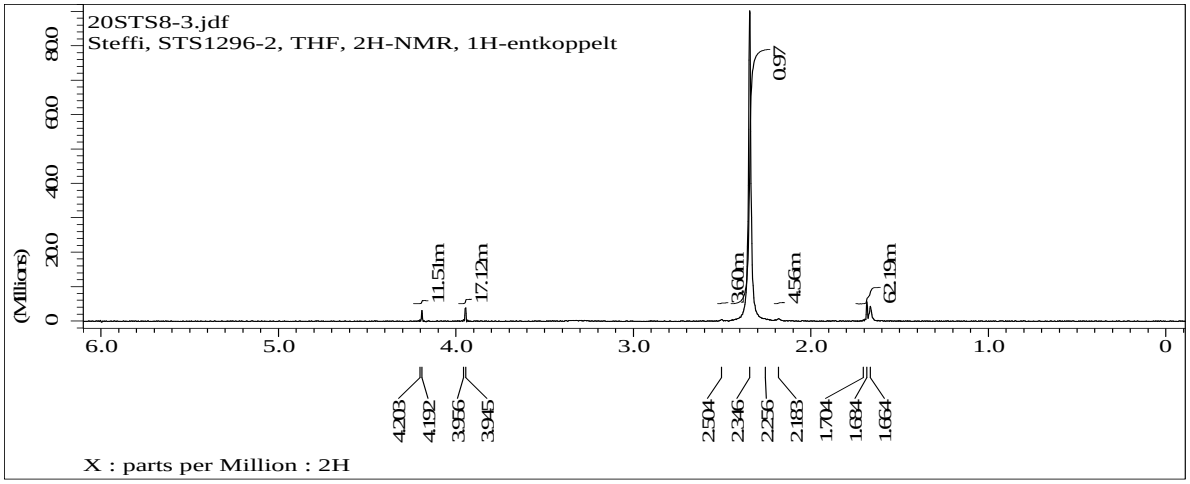
from **108** (deuterolysis at rt with d-TFA):



d.r.: 69:31.
^{2}H-NMR (61 MHz, THF) δ: 2.34 (s, 1 D) (major), 1.58 (s, 1 D) (minor).

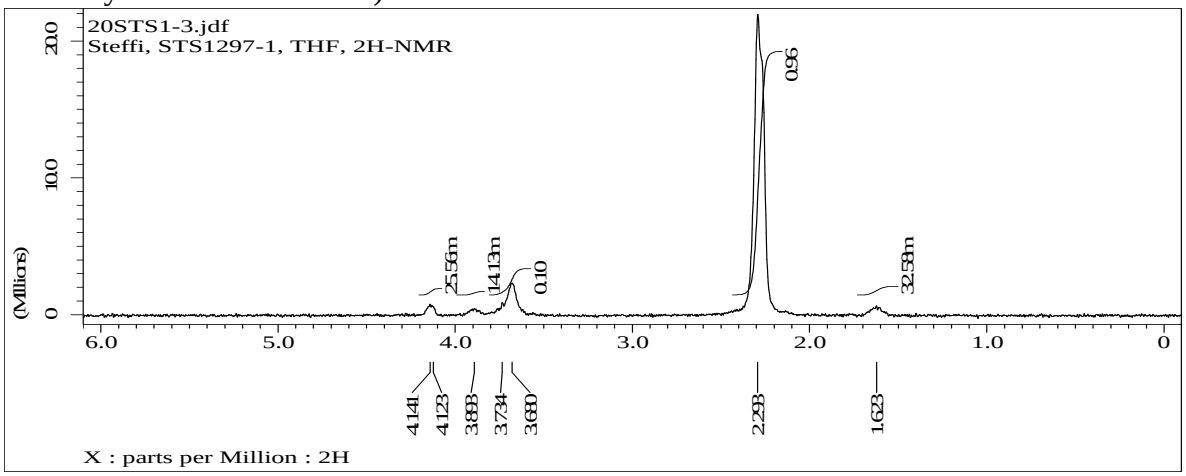
(deuterolysis at -78 ^{o}C with d-TFA)

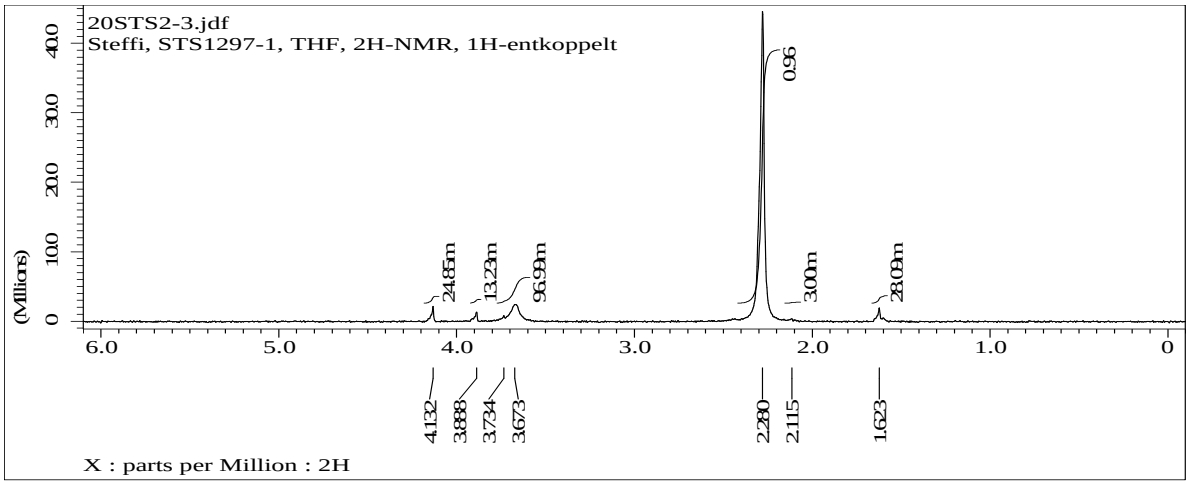




d.r.: 99:1.
^{2}H-NMR (61 MHz, THF) δ: 2.34 (s, 1 D) (major), 1.68 (s, 1 D) (minor).

(deuterolysis at rt with MeOD)



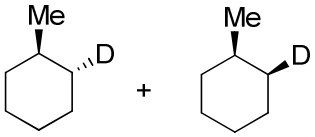


d.r.: 99:1.

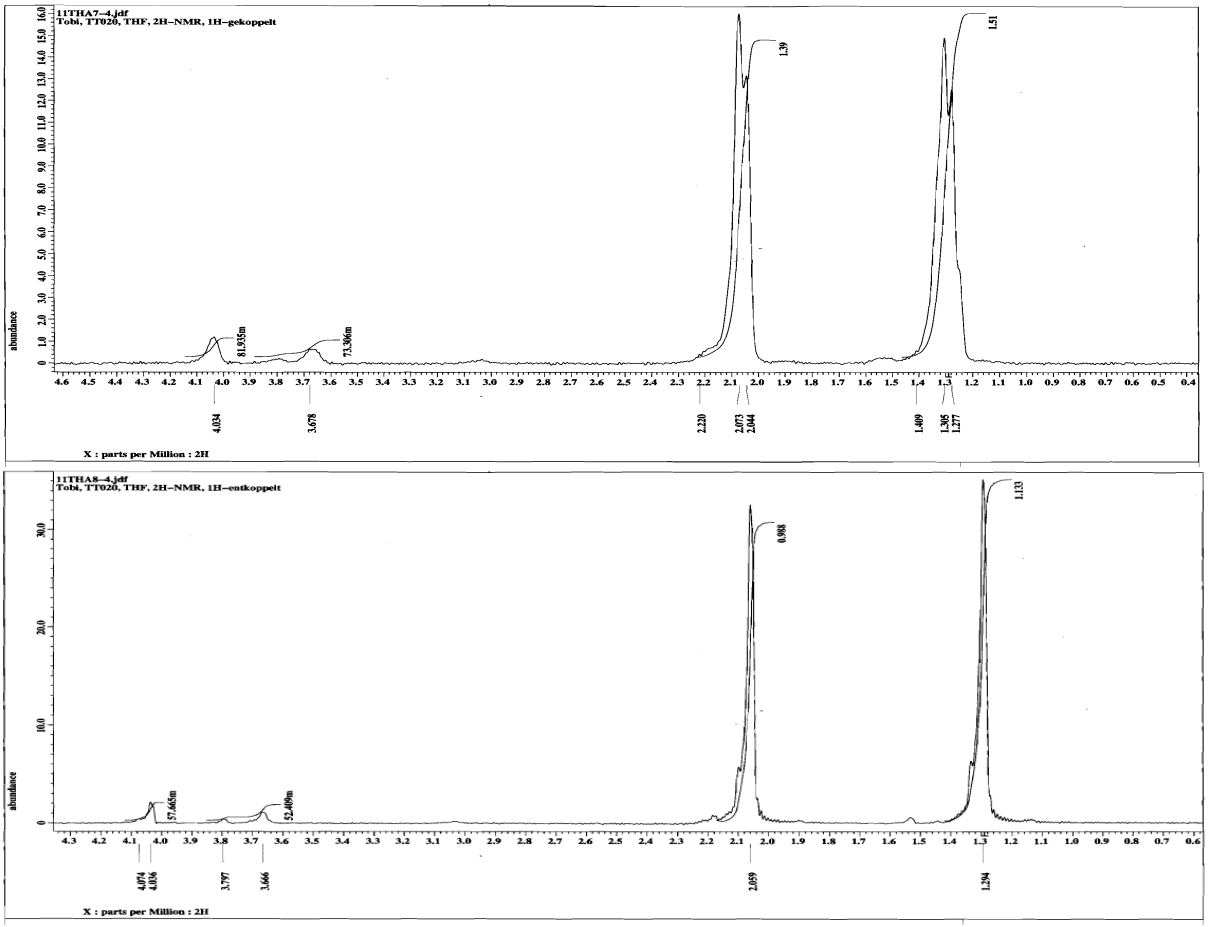
^{2}H-NMR (61 MHz, THF) δ: 2.30 (s, 1 D) (major), 1.62 (s, 1 D) (minor).

trans-methyl(2-$^2H_1$)cyclohexane (_trans_-(_eq_)-116)

& _cis_-methyl(2-$^2H_1$)cyclohexane (_cis_-(_eq_)-116)



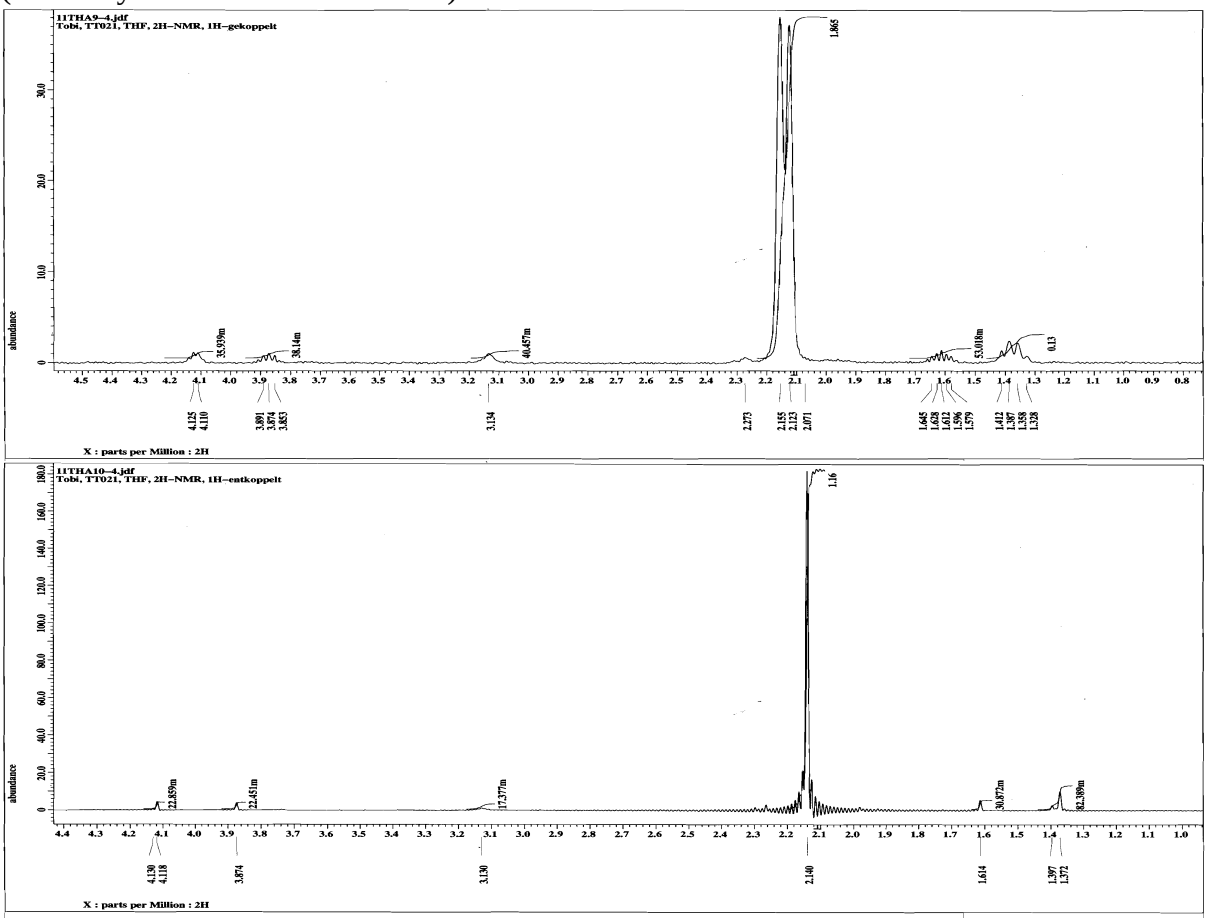
(deuterolysis at rt with d-TFA)



d.r.: 48:52.

^{2}H-NMR (61 MHz, THF) δ: 2.11 (s, 1 D) (major), 1.33 (s, 1 D) (minor).

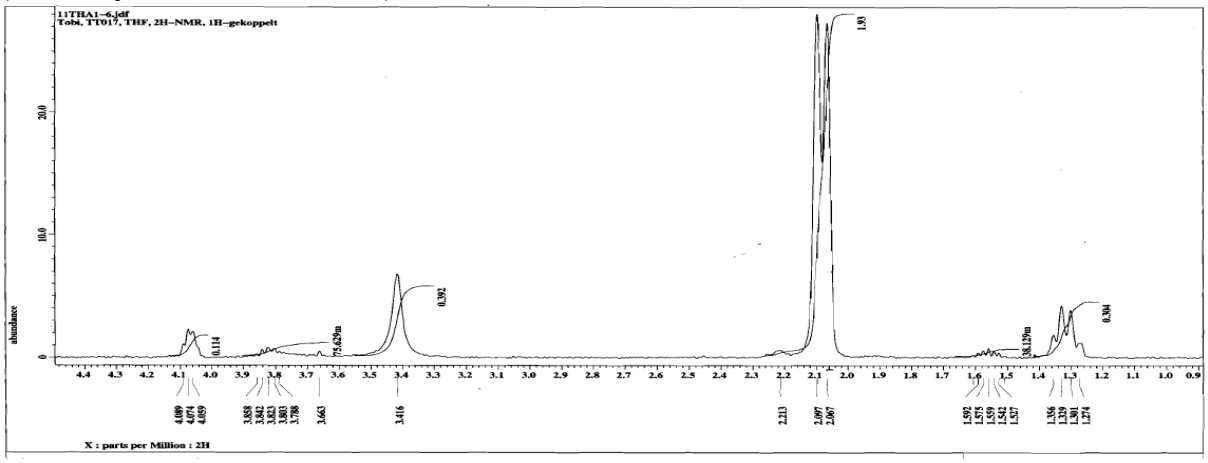
(deuterolysis at -78 °C with d-TFA)

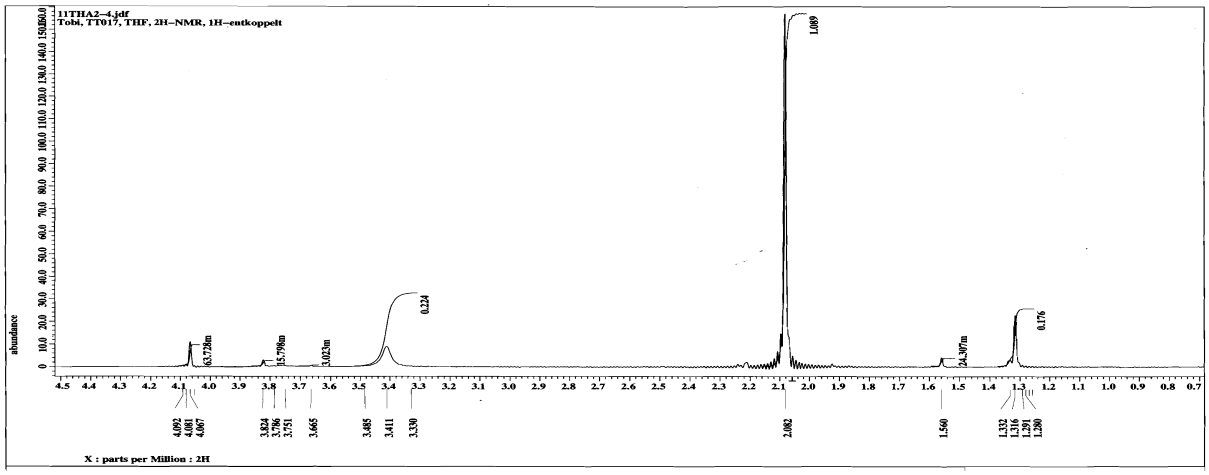


d.r.: 96:4.

^{2}H-NMR (61 MHz, THF) δ: 2.11 (s, 1 D) (major), 1.37 (s, 1 D) (minor).

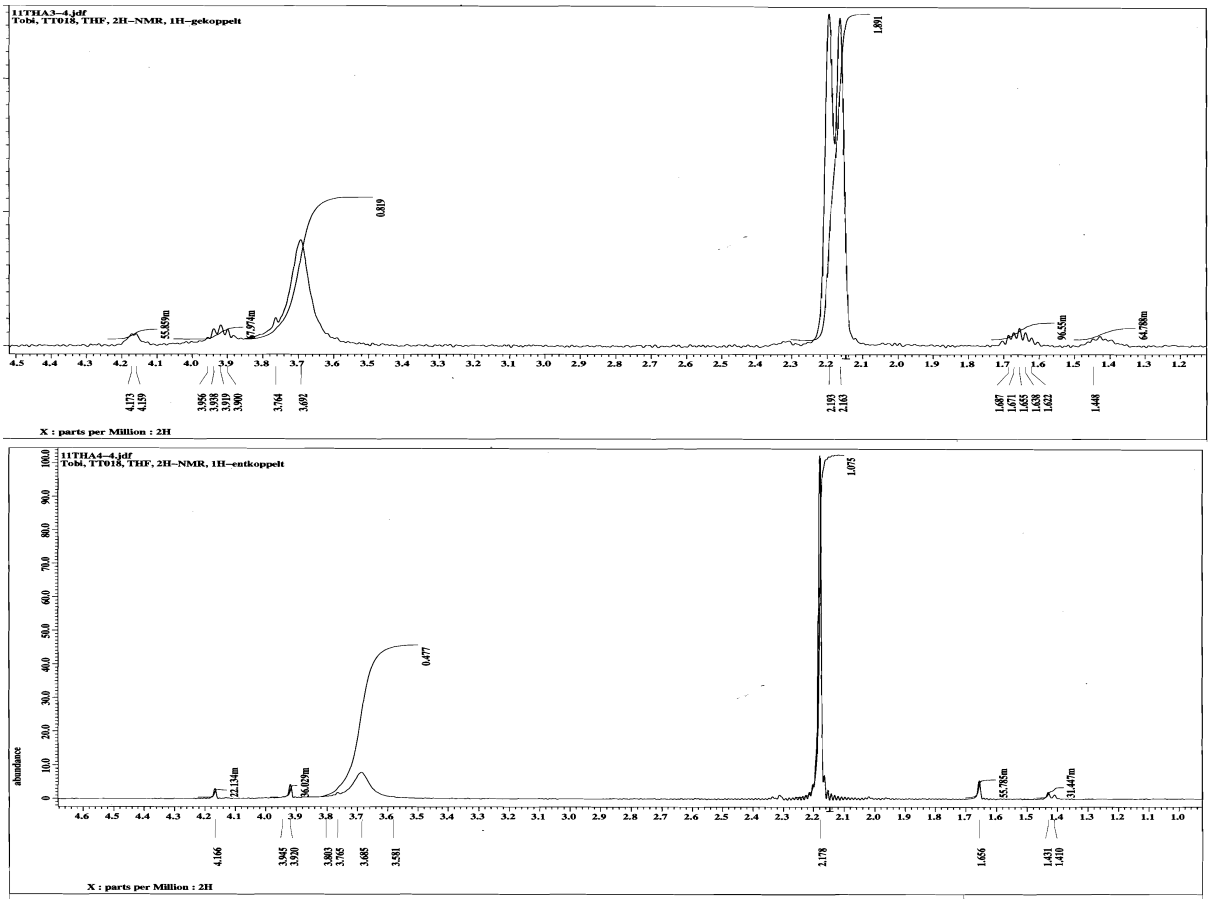
(deuterolysis at rt with MeOD)





d.r.: 87:13.
^{2}H-NMR (61 MHz, THF) δ: 2.10 (s, 1 D) (major), 1.32 (s, 1 D) (minor).

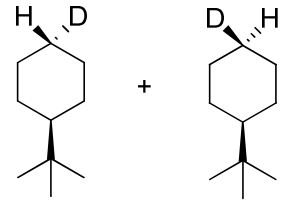
(deuterolysis at 0°C with MeOD)



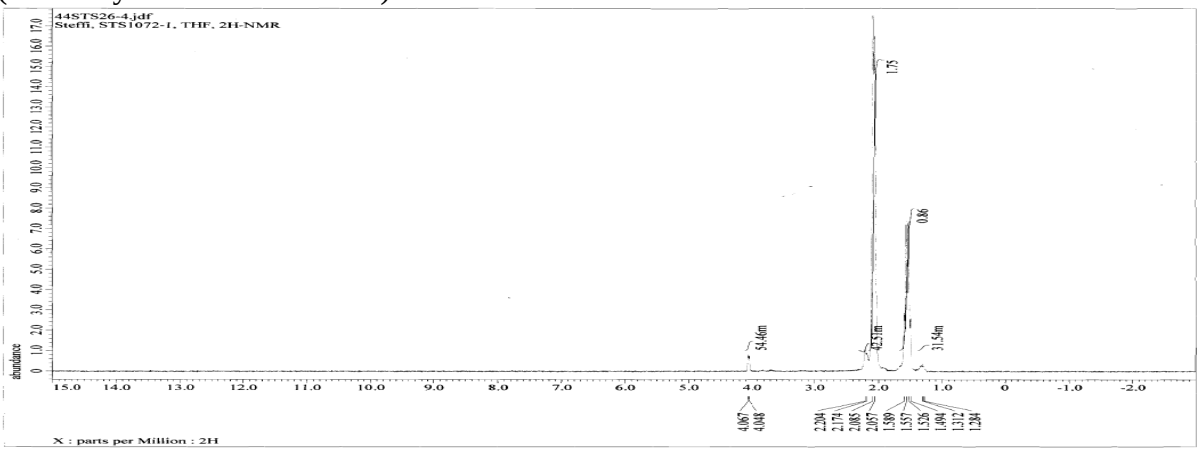
d.r.: 97:3.
^{2}H-NMR (61 MHz, THF) δ: 2.18 (s, 1 D) (major), 1.45 (s, 1 D) (minor).

trans-_tert_-butyl(4-$^2H_1$)cyclohexane (_trans_-(_eq_)-117)

& _cis_-1-(_tert_-butyl)-4-deuterocyclohexane (_cis_-(_eq_)-117)



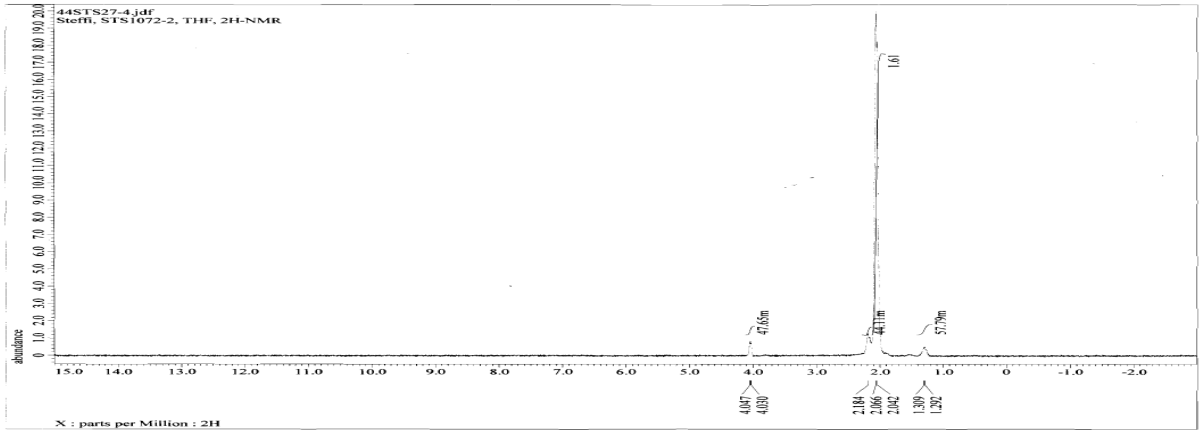
(deuterolysis at rt with d-TFA)



d.r.: 67:33.

^{2}H-NMR (61 MHz, THF) δ: 2.07 (s, 1 D) (major), 1.54 (s, 1 D) (minor).

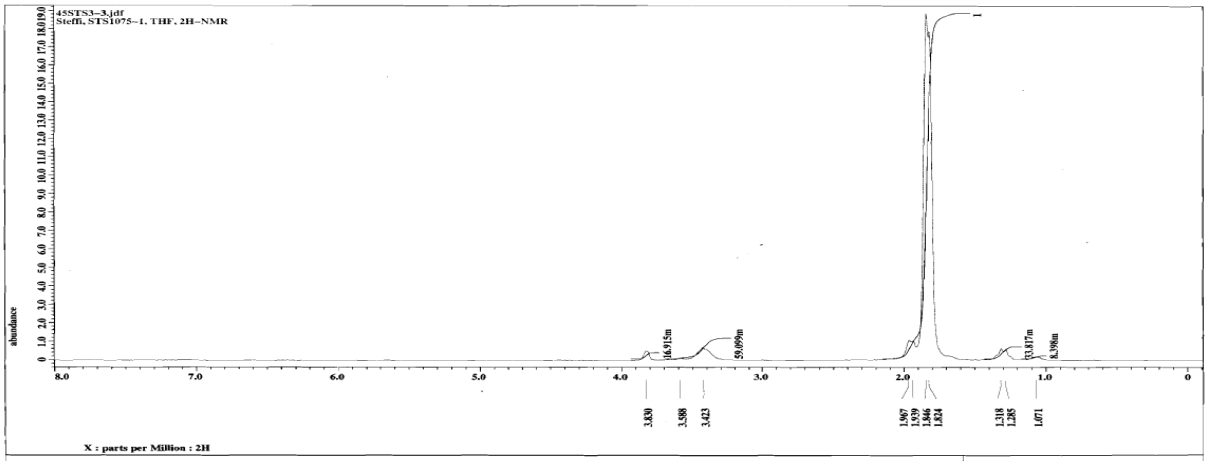
(deuterolysis at -78 ^oC with d-TFA)



d.r.: >99:1.

^{2}H-NMR (61 MHz, THF) δ: 2.05 (s, 1 D) (major), 1.30 (s, 1 D) (minor).

(deuterolysis at rt with MeOD)

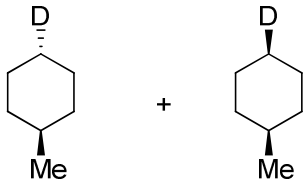


d.r.: >99:1.

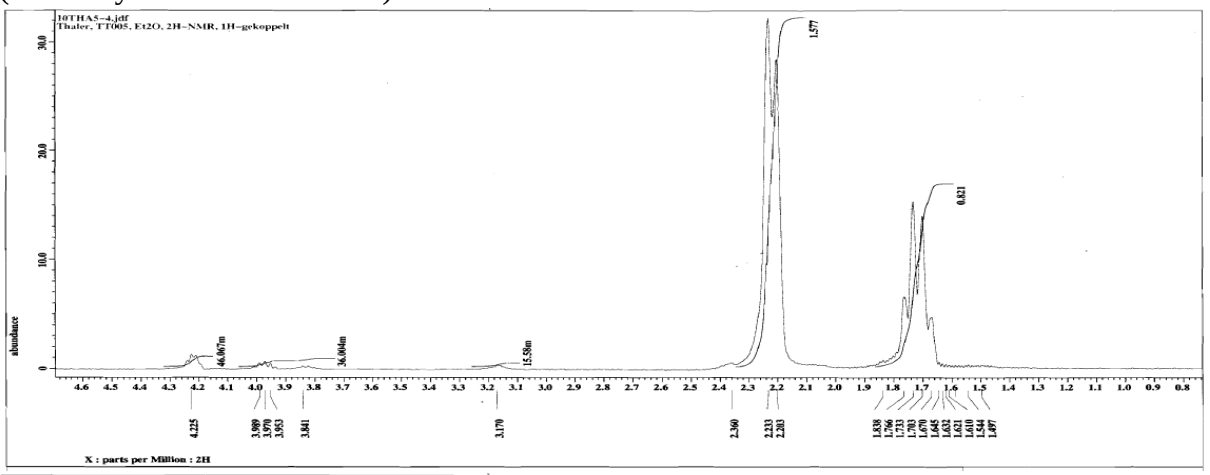
^{2}H-NMR (61 MHz, THF) δ: 1.90 (s, 1 D) (major), 1.30 (s, 1 D) (minor).

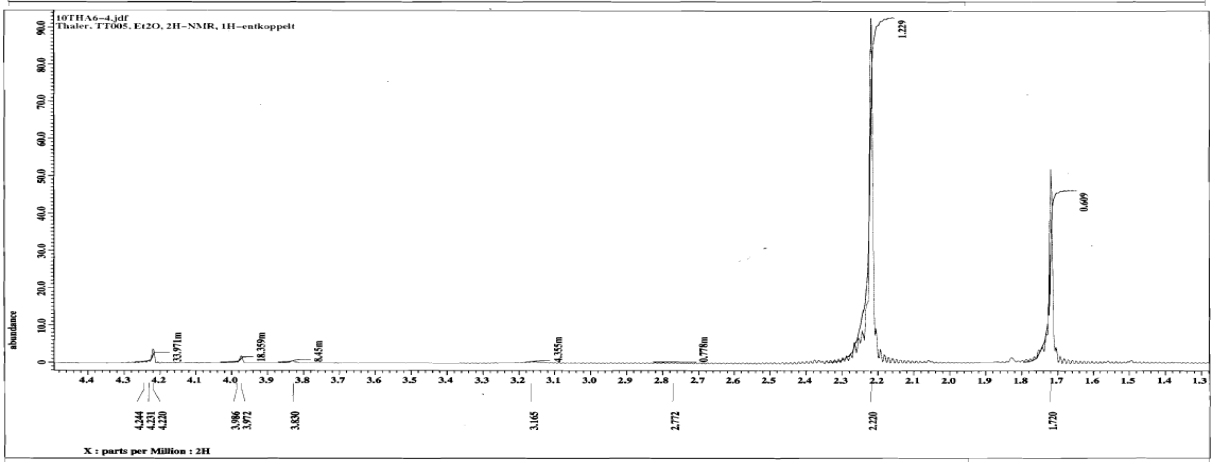
trans-methyl(4-$^2H_1$)cyclohexane (_trans_-(_eq_)-119)

& _cis_-methyl(4-$^2H_1$)cyclohexane (_cis_-(_eq_)-119)



(deuterolysis at rt with d-TFA)

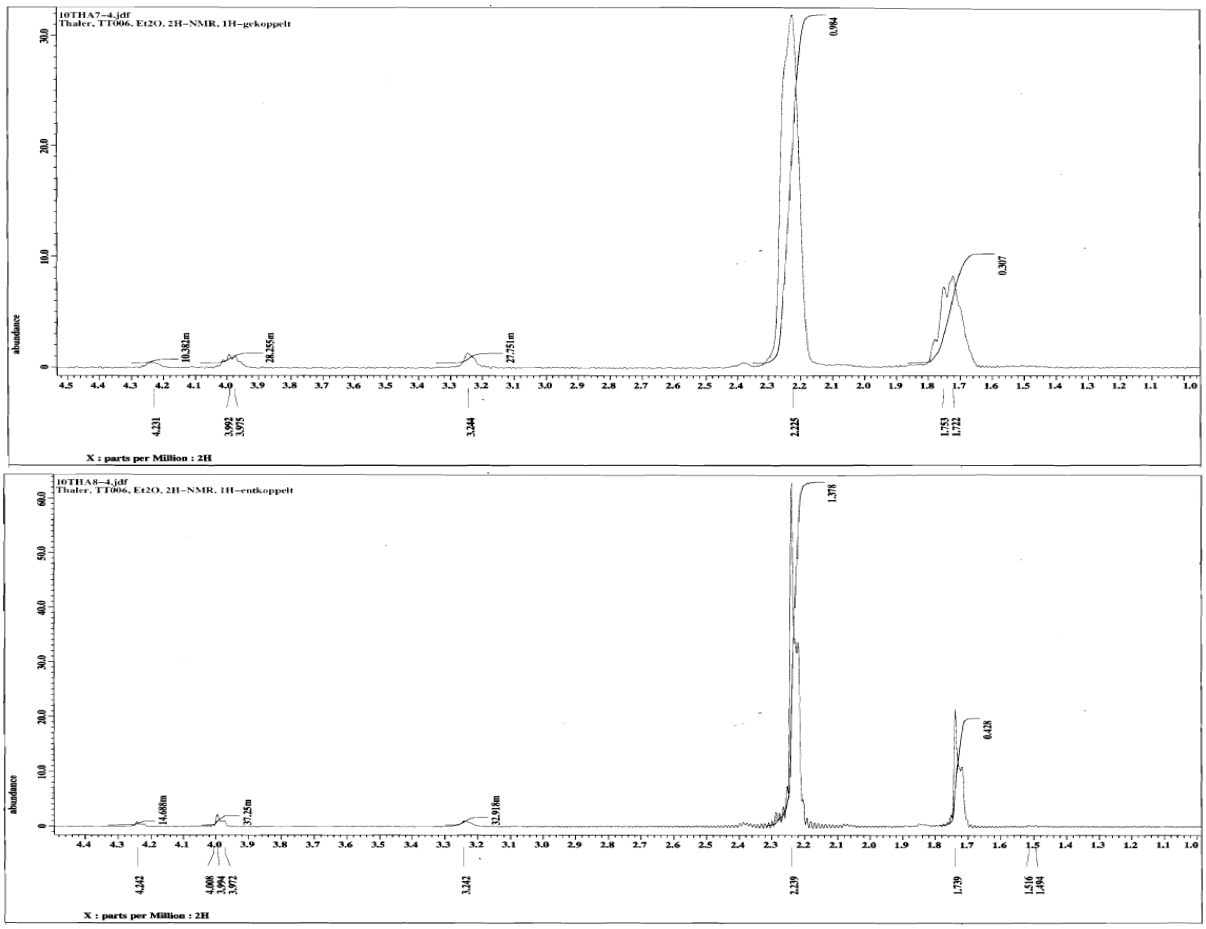




d.r.: 66:34.

^{2}H-NMR (61 MHz, THF) δ: 2.27 (s, 1 D) (major), 1.67 (s, 1 D) (minor).

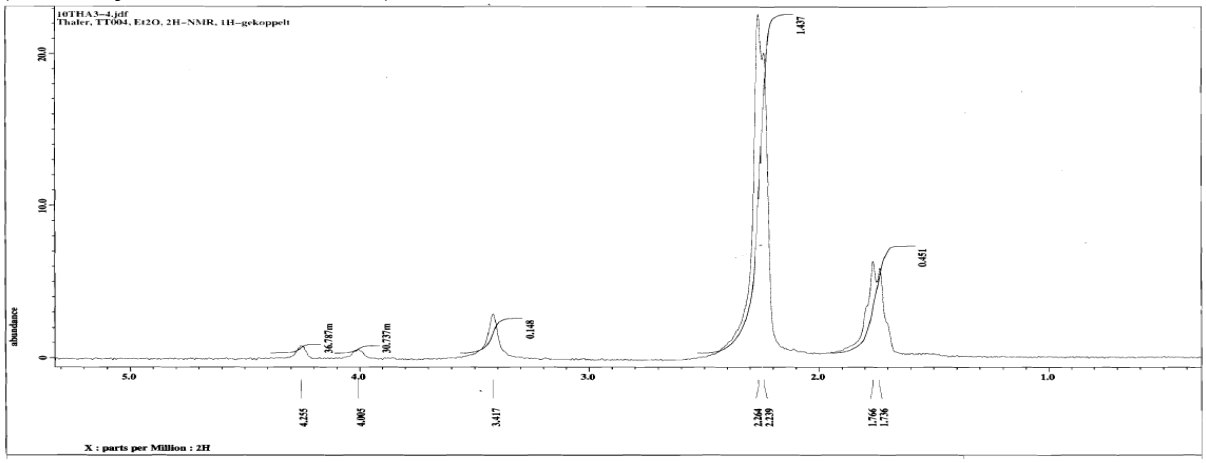
(deuterolysis at -78 ^{o}C with d-TFA)

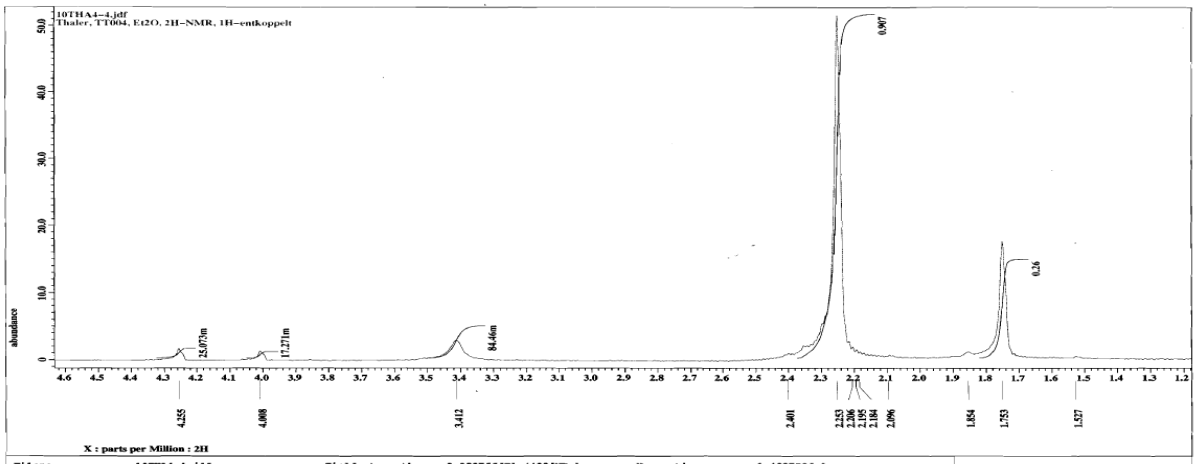


d.r.: 76:24.

^{2}H-NMR (61 MHz, THF) δ: 2.23 (s, 1 D) (major), 1.74 (s, 1 D) (minor).

(deuterolysis at rt with MeOD)

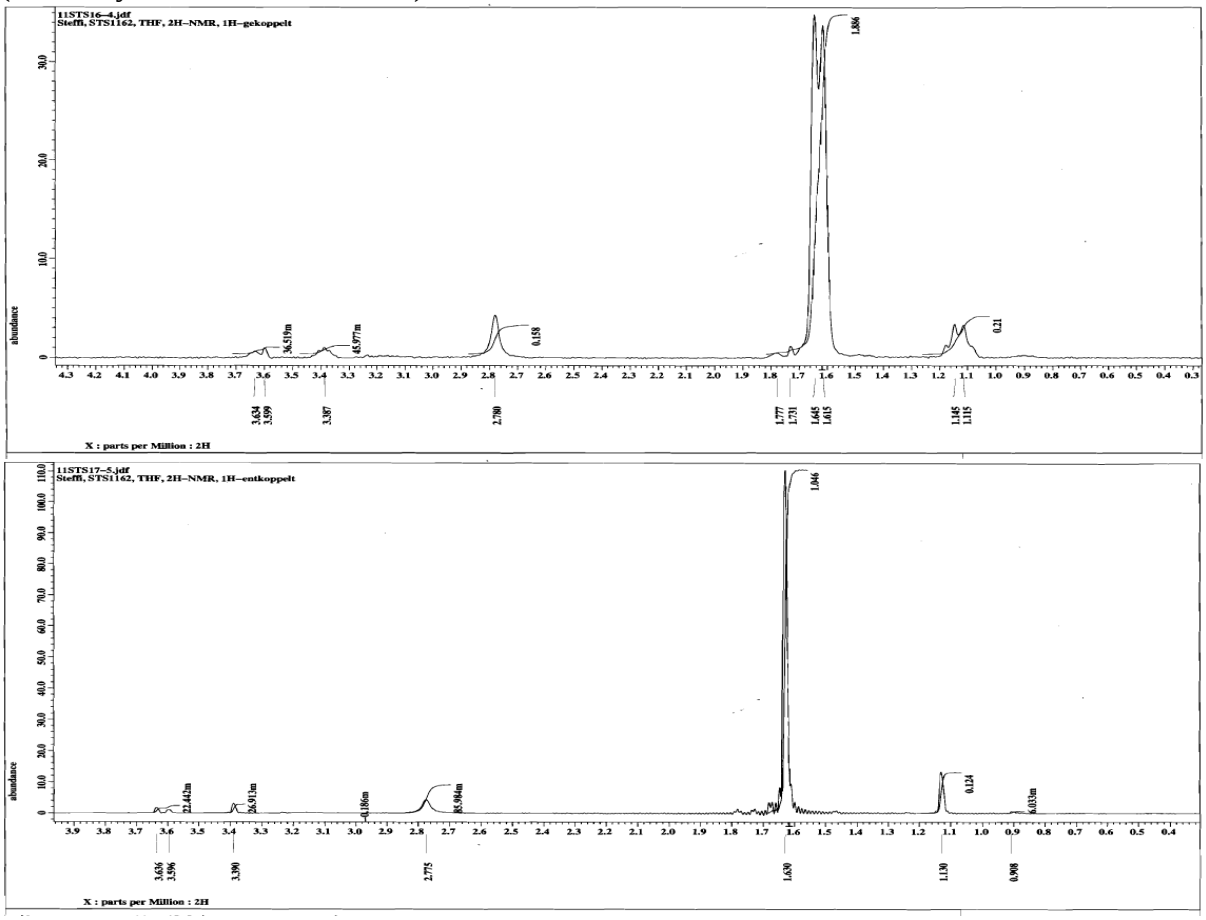




d.r.: 76:24.

^{2}H-NMR (61 MHz, THF) δ: 2.25 (s, 1 D) (major), 1.75 (s, 1 D) (minor).

(deuterolysis at 0^{o}C with MeOD)

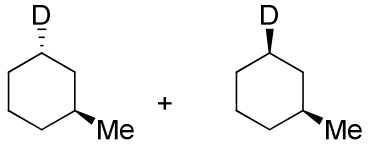


d.r.: 90:10.

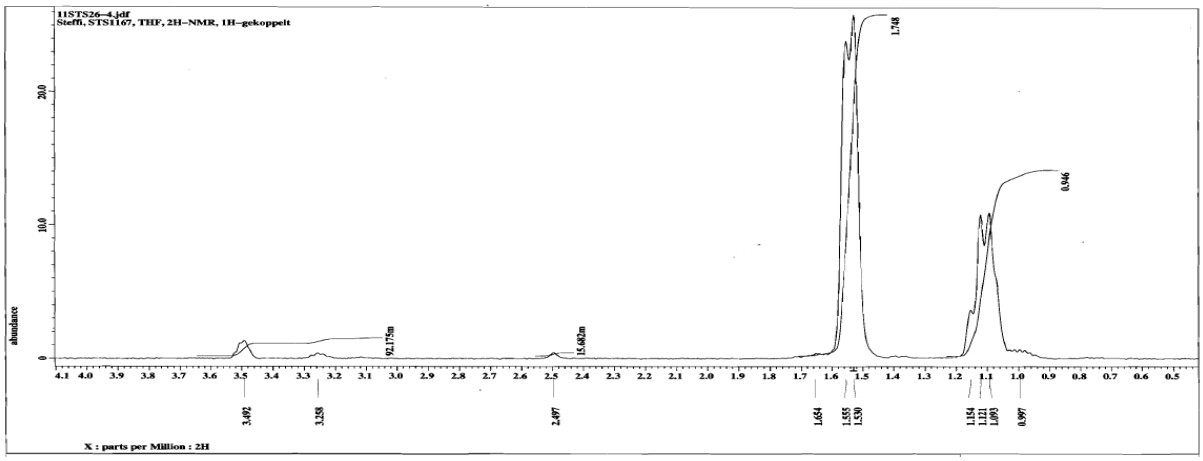
^{2}H-NMR (61 MHz, THF) δ: 1.69 (s, 1 D) (major), 1.13 (s, 1 D) (minor).

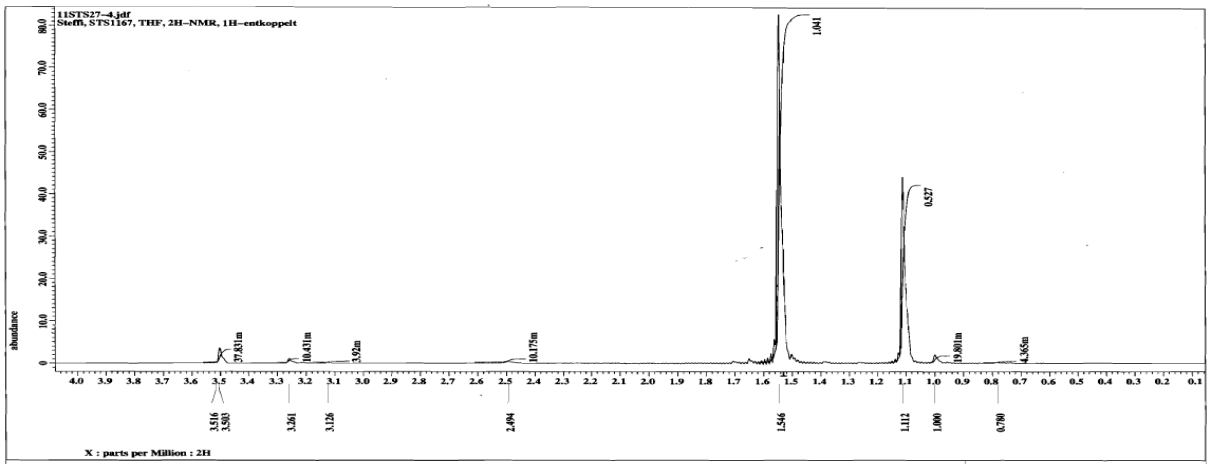
trans-methyl(3-$^2H_1$)cyclohexane (_cis_-(_eq_)-121)

& _cis_- methyl(3-$^2H_1$)cyclohexane (_trans_-(_eq_)-121)



(deuterolysis at rt with d-TFA)

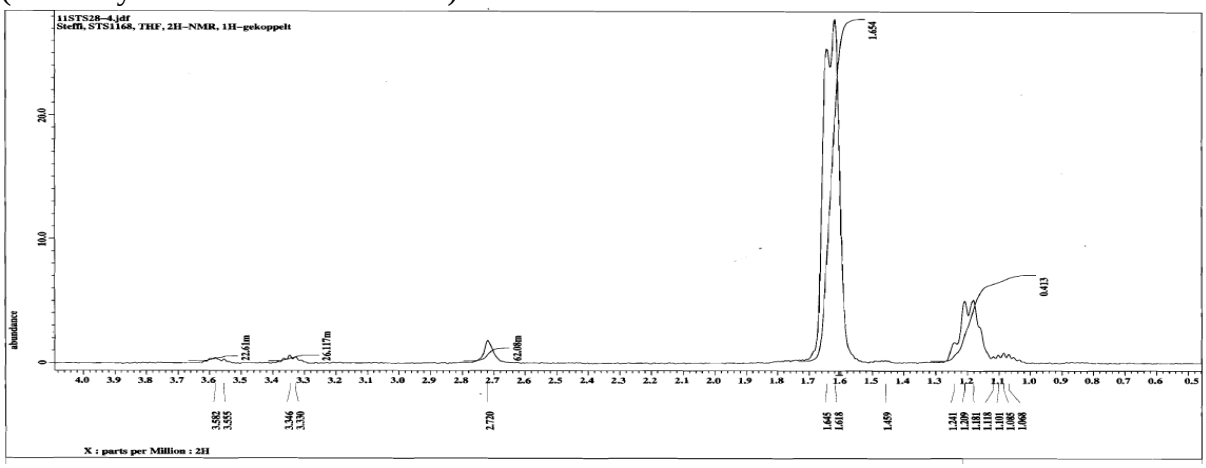


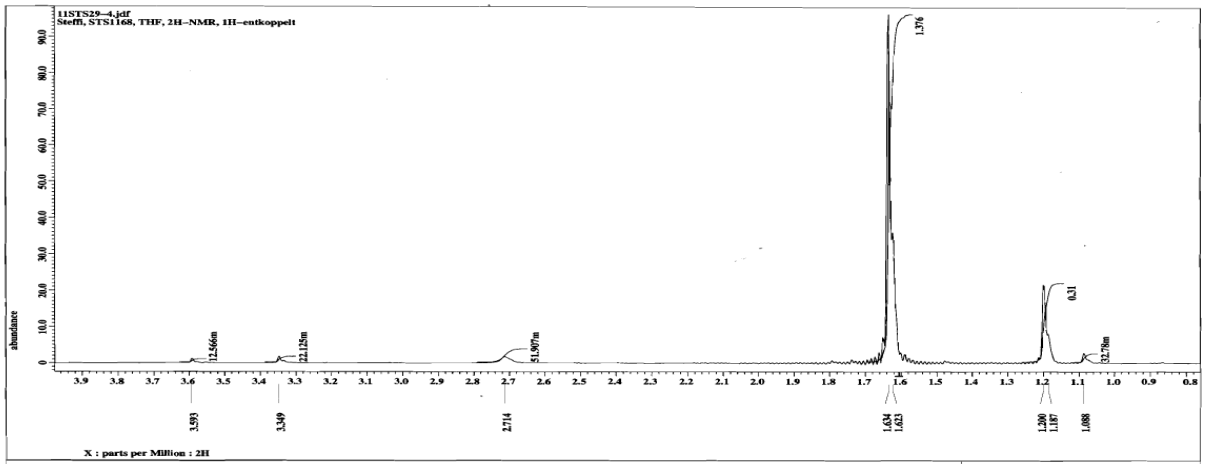


d.r.: 65:35.

^{2}H-NMR (61 MHz, THF) δ: 1.54 (s, 1 D) (major), 1.12 (s, 1 D) (minor).

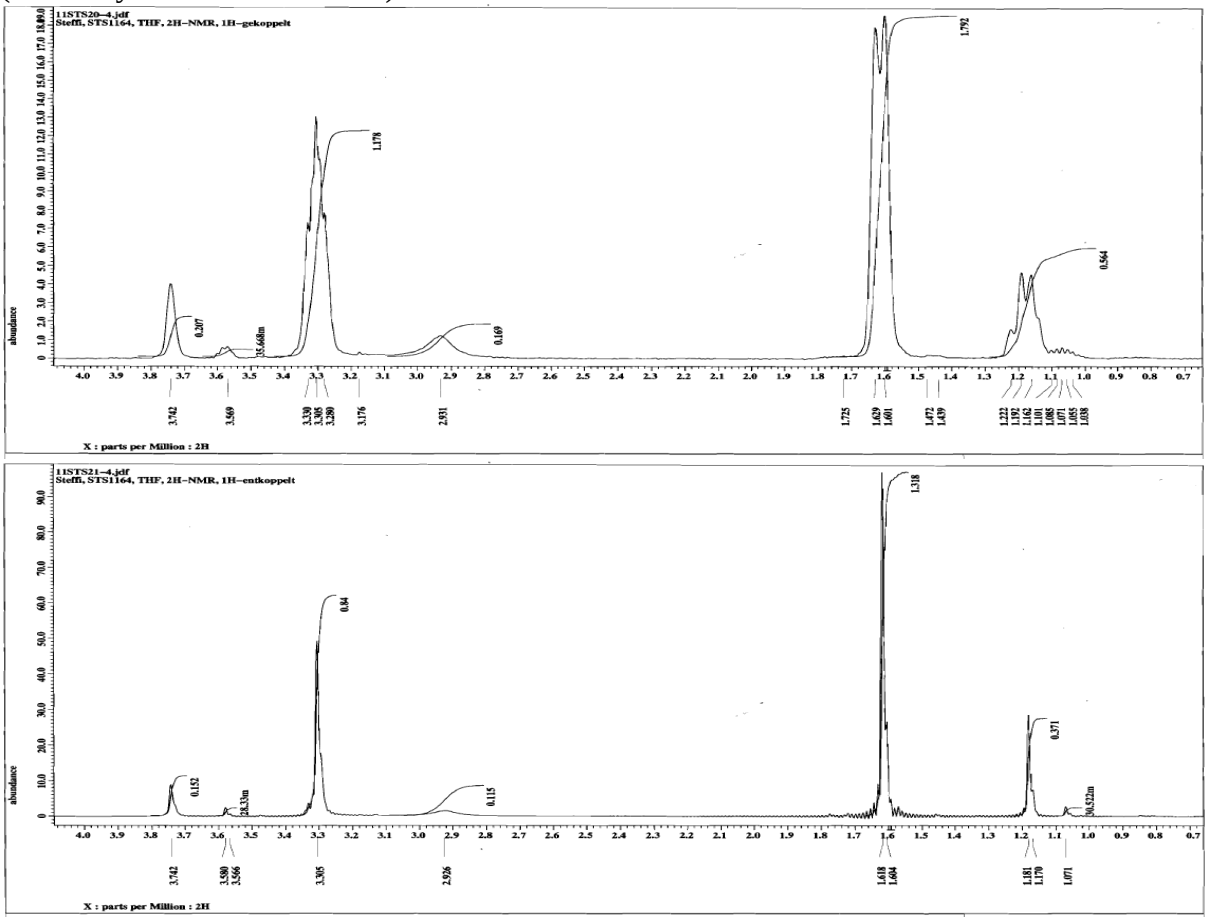
(deuterolysis at -78 ^{o}C with d-TFA)





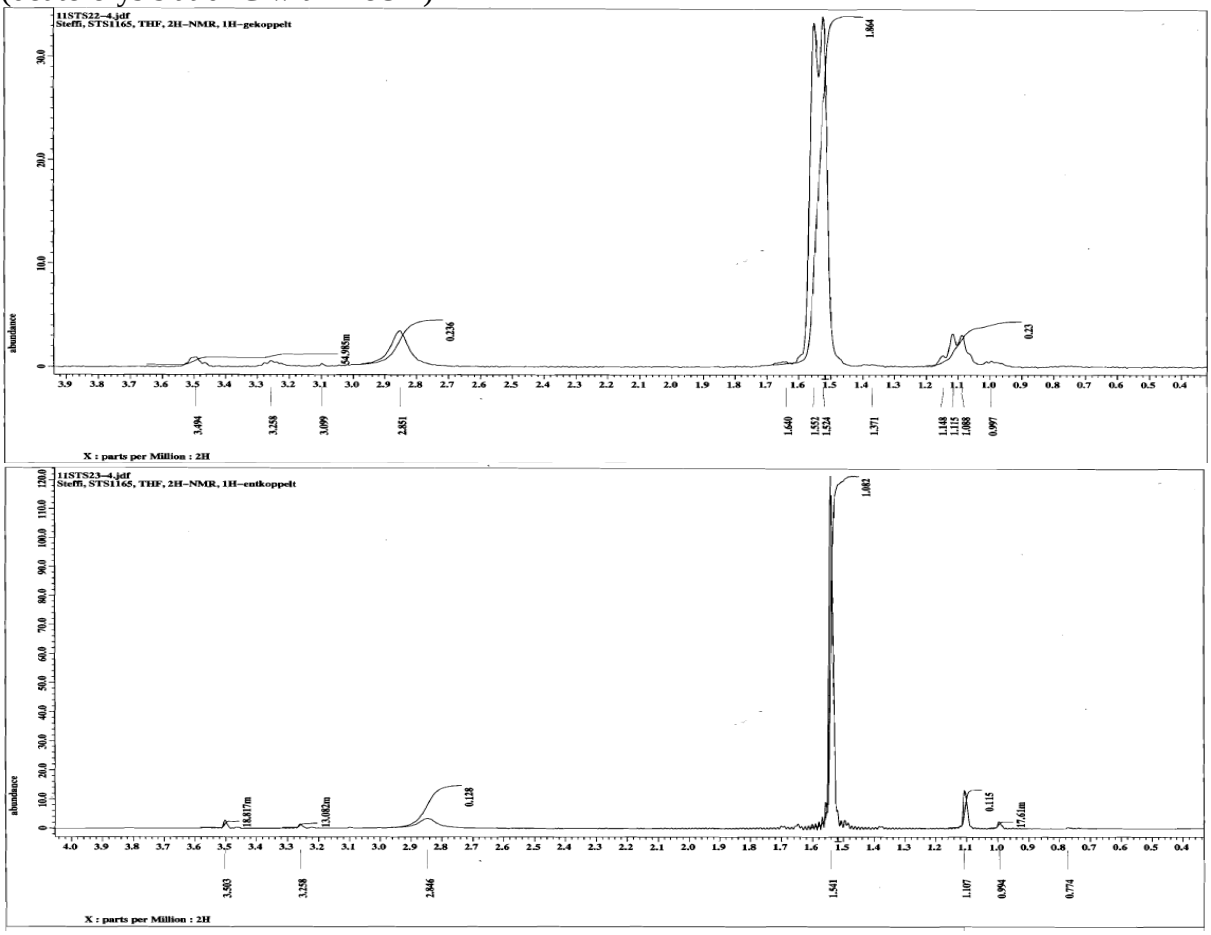
d.r.: 80:20.
^{2}H-NMR (61 MHz, THF) δ: 1.63 (s, 1 D) (major), 1.21 (s, 1 D) (minor).

(deuterolysis at rt with MeOD)



d.r.: 76:24.
^{2}H-NMR (61 MHz, THF) δ: 1.62 (s, 1 D) (major), 1.19 (s, 1 D) (minor).

(deuterolysis at 0 °C with MeOD)

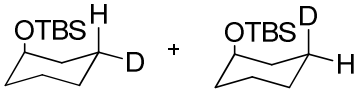


d.r.: 90:10.

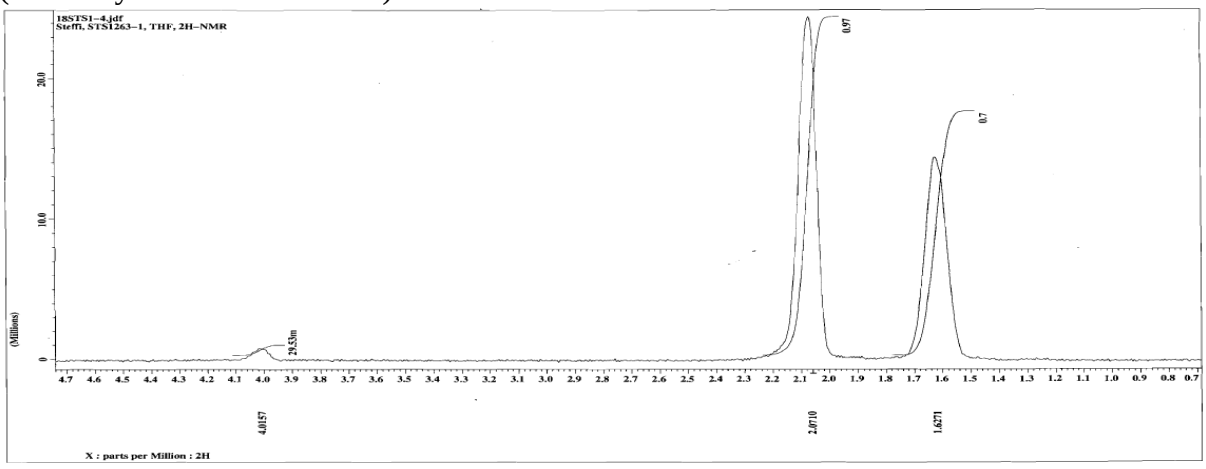
^{2}H-NMR (61 MHz, THF) δ: 1.54 (s, 1 D) (major), 1.12 (s, 1 D) (minor).

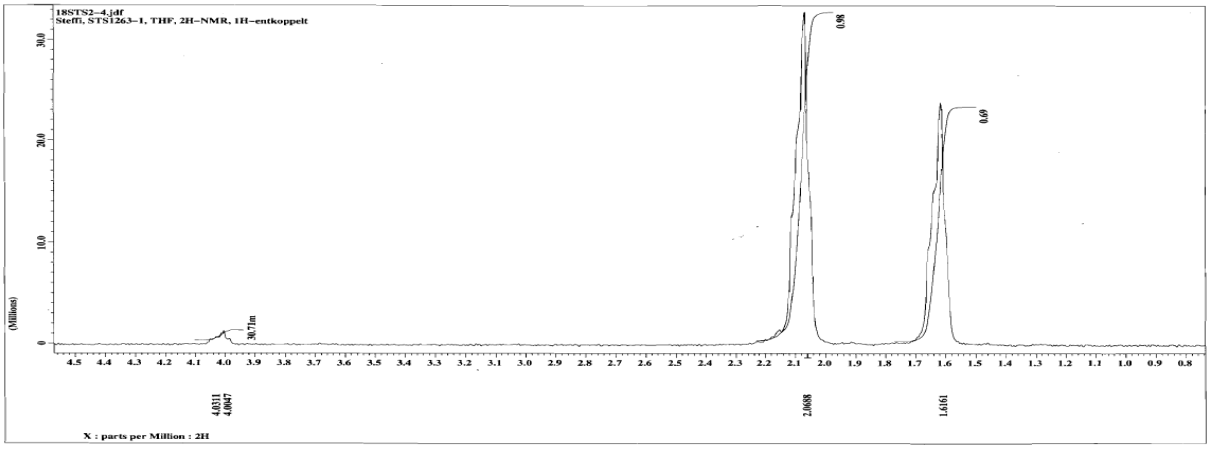
***trans-tert*-butyldimethyl(((3-$^2H_1$)cyclohexyl)oxy)silane (*cis*-(*eq*)-123)**

& *cis- tert*-butyldimethyl(((3-$^2H_1$)cyclohexyl)oxy)silane (*trans*-(*eq*)-123)



(deuterolysis at rt with d-TFA)

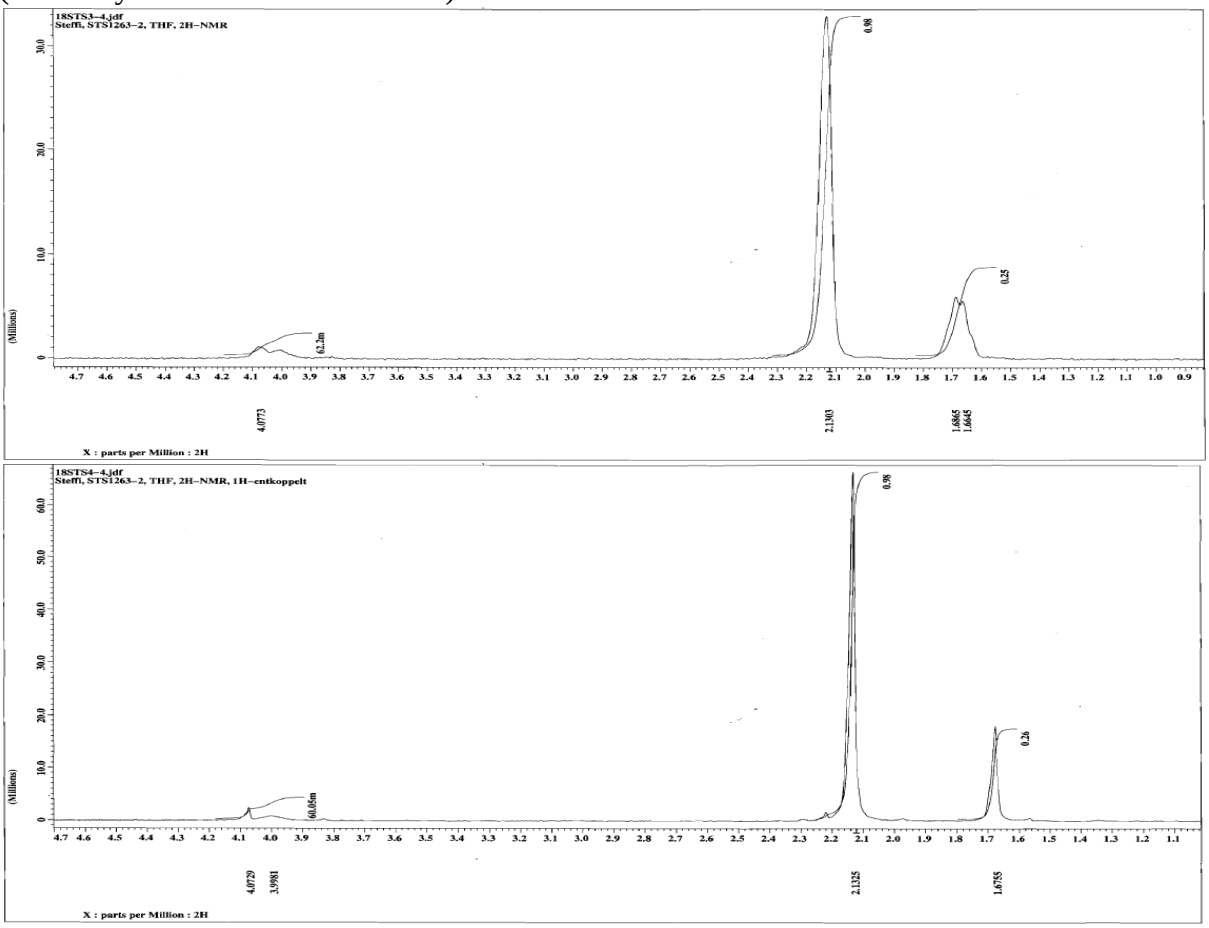




d.r.: 58:42.

^{2}H-NMR (61 MHz, THF) δ: 2.07 (s, 1 D) (major), 1.63 (s, 1 D) (minor).

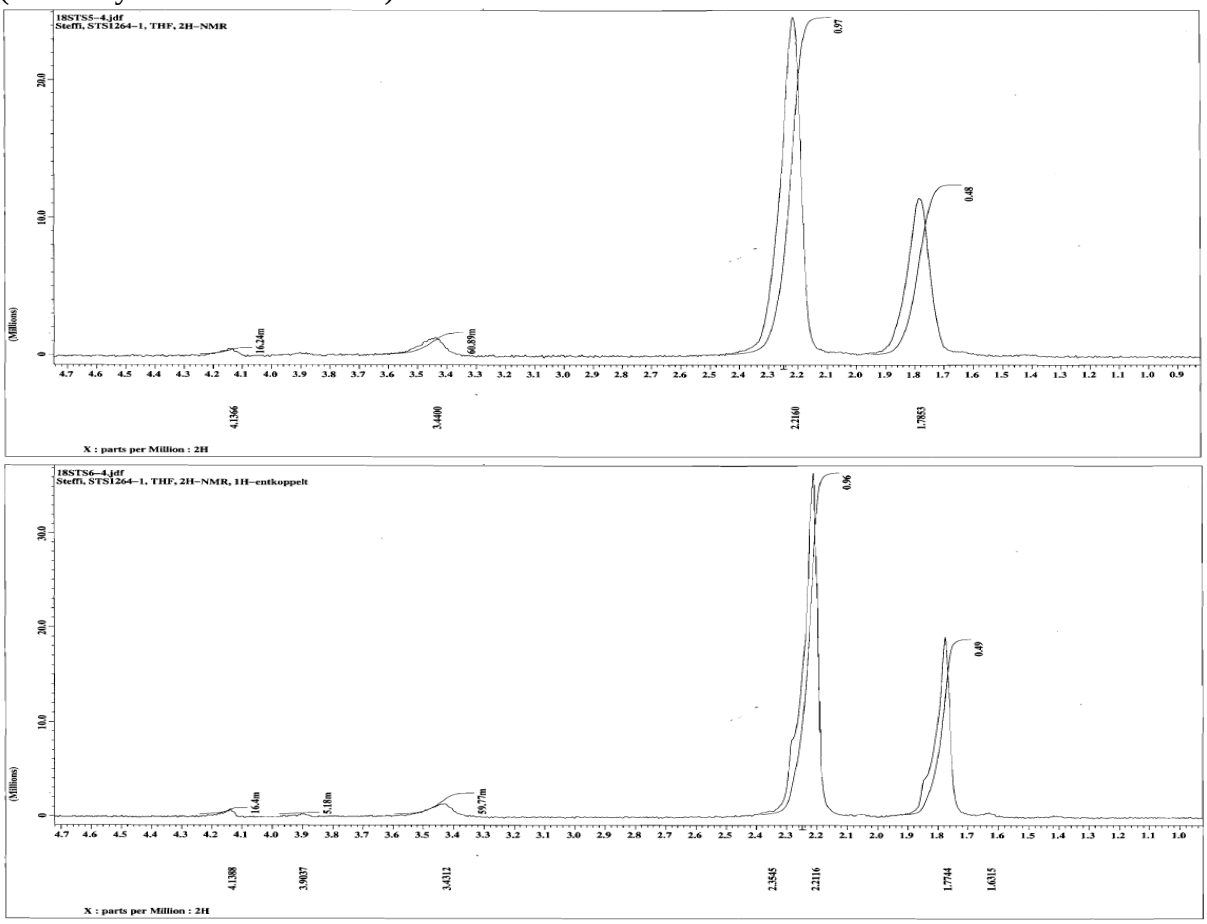
(deuterolysis at -78 ^{o}C with d-TFA)



d.r.: 79:21.

^{2}H-NMR (61 MHz, THF) δ: 2.13 (s, 1 D) (major), 1.68 (s, 1 D) (minor).

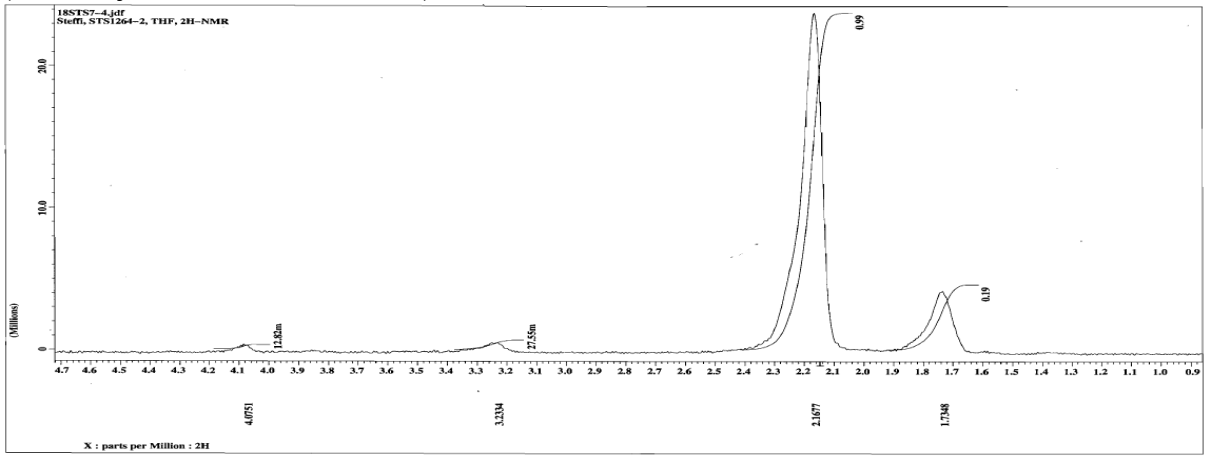
(deuterolysis at rt with MeOD)

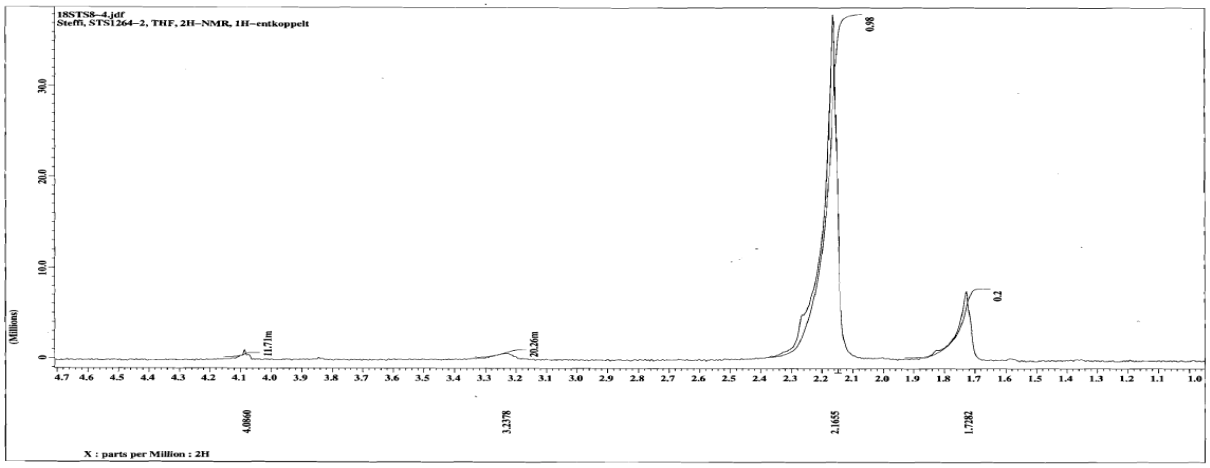


d.r.: 66:44.

^{2}H-NMR (61 MHz, THF) δ: 2.22 (s, 1 D) (major), 1.79 (s, 1 D) (minor).

(deuterolysis at 0 ^{o}C with MeOD)

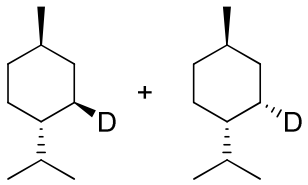




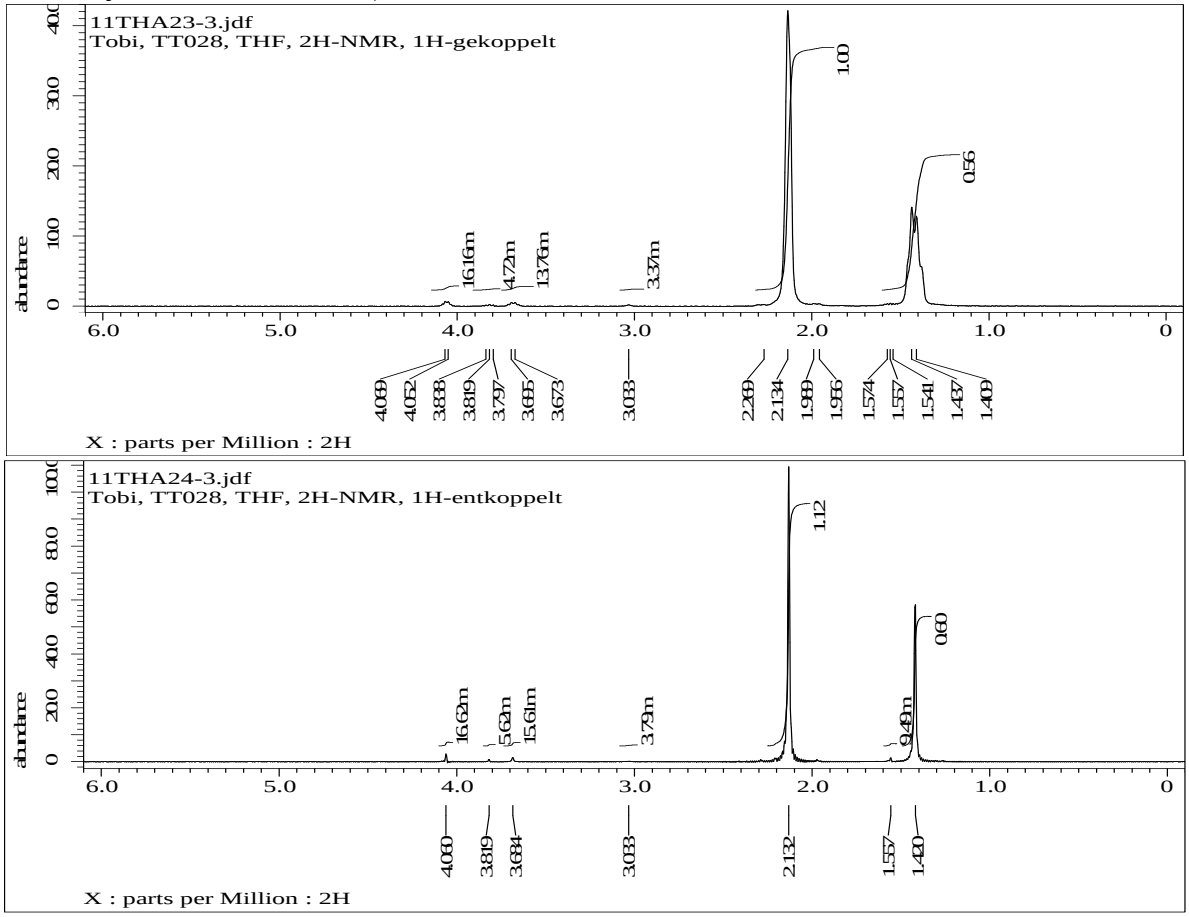
d.r.: 84:16.
^{2}H-NMR (61 MHz, THF) δ: 2.17 (s, 1 D) (major), 1.73 (s, 1 D) (minor).

(1*R*,2*R*,4*R*)-4-methyl-1-(1-methylethyl)(2-$^2H_1$)cyclohexane (*men*-(*eq*)-125)

& (1*R*,2*S*,4*R*)-4-methyl-1-(1-methylethyl)(2-$^2H_1$)cyclohexane (neo*men*-(*ax*)-125)



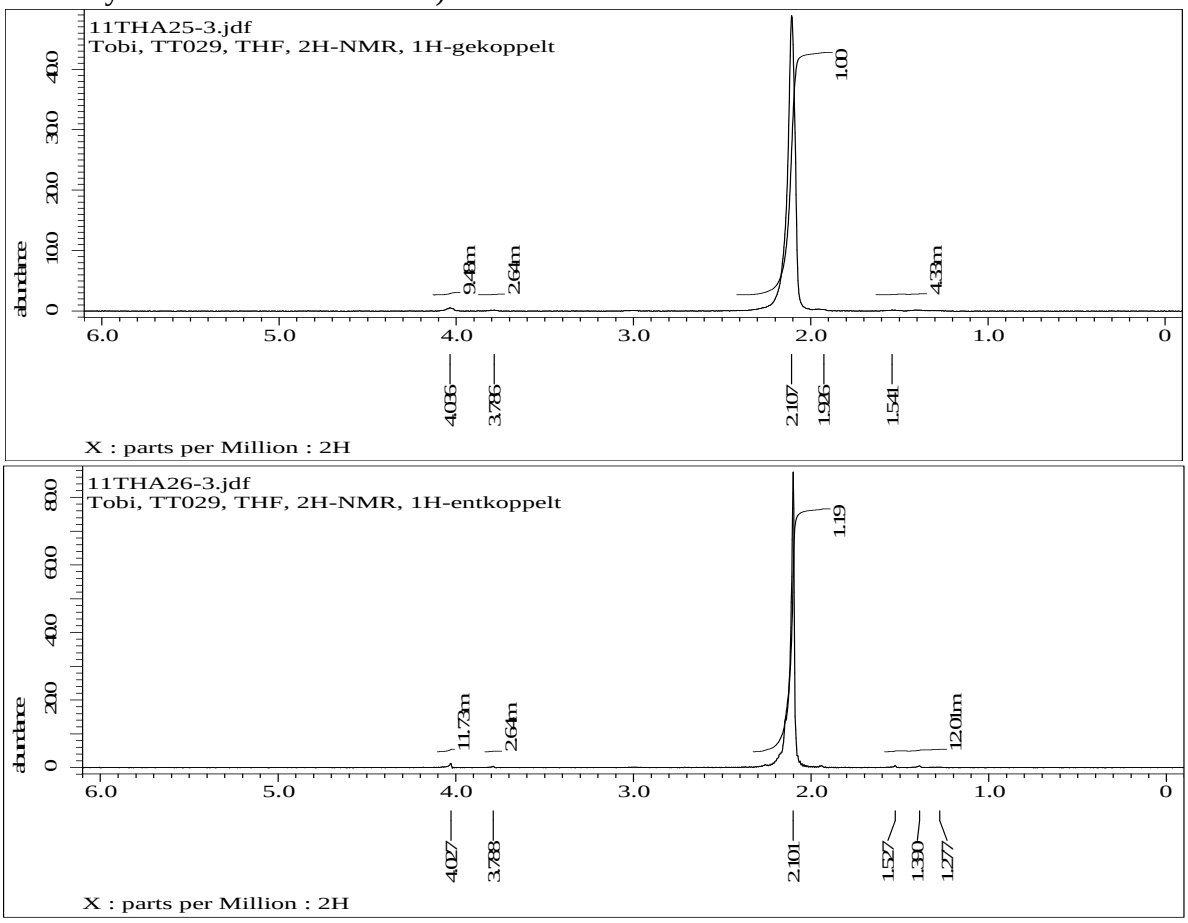
(deuterolysis at rt with d-TFA)



d.r.: 65:35.

^{2}H-NMR (61 MHz, THF) δ: 2.13 (s, 1 D) (major), 1.43 (s, 1 D) (minor).

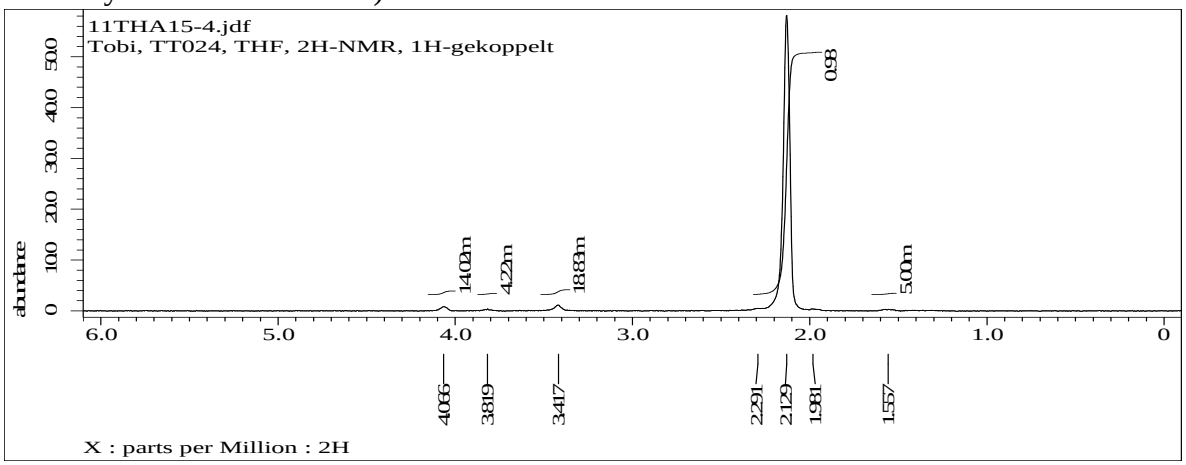
(deuterolysis at -78 ^{o}C with d-TFA)

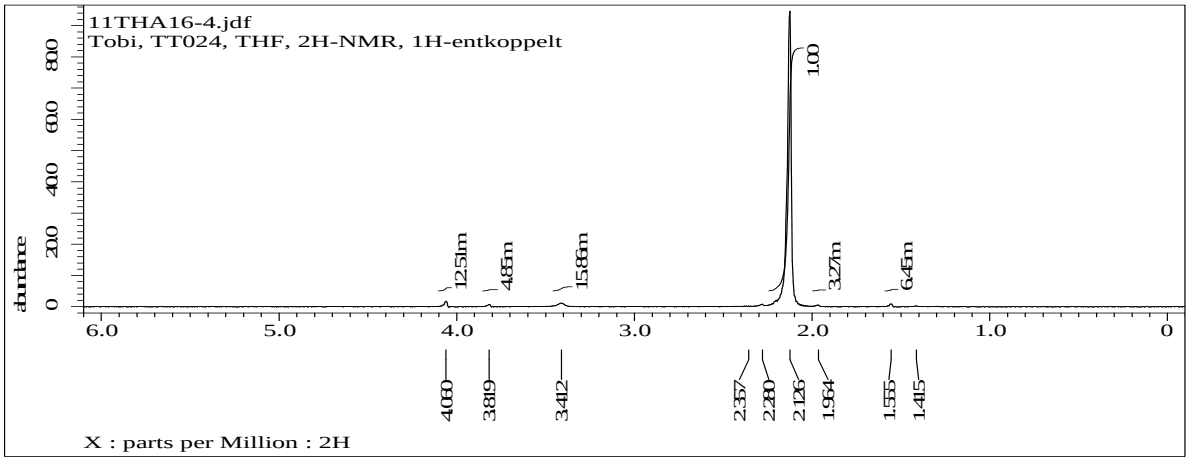


d.r.: >99:1.

^{2}H-NMR (61 MHz, THF) δ: 2.10 (s, 1 D) (major), 1.39 (s, 1 D) (minor).

(deuterolysis at rt with MeOD)



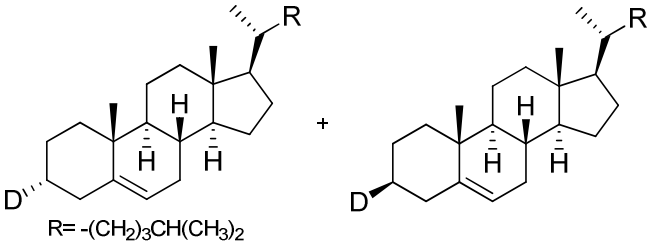


d.r.: >99:1.

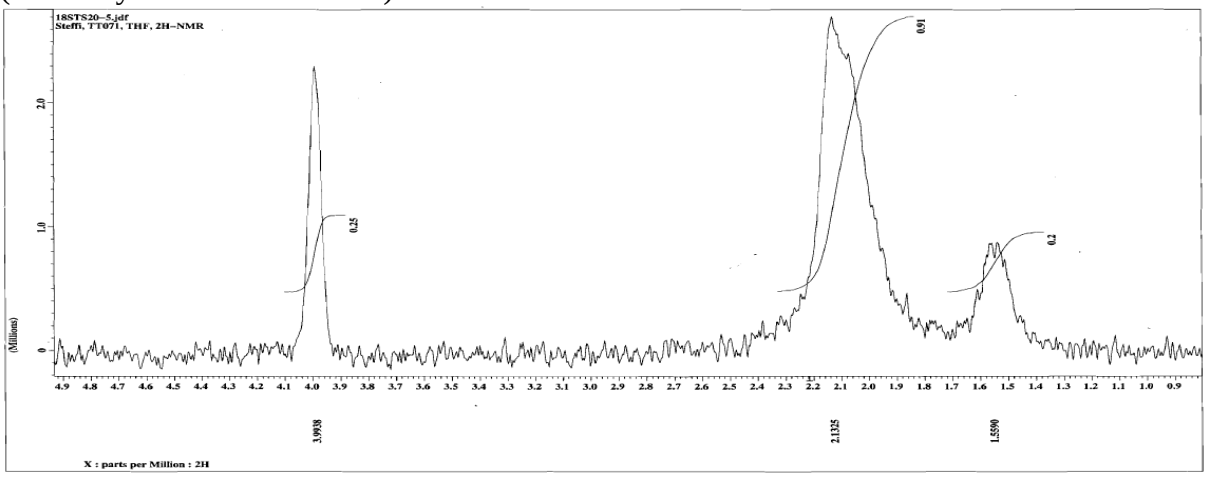
^{2}H-NMR (61 MHz, THF) δ: 2.13 (s, 1 D) (major), 1.56 (s, 1 D) (minor).

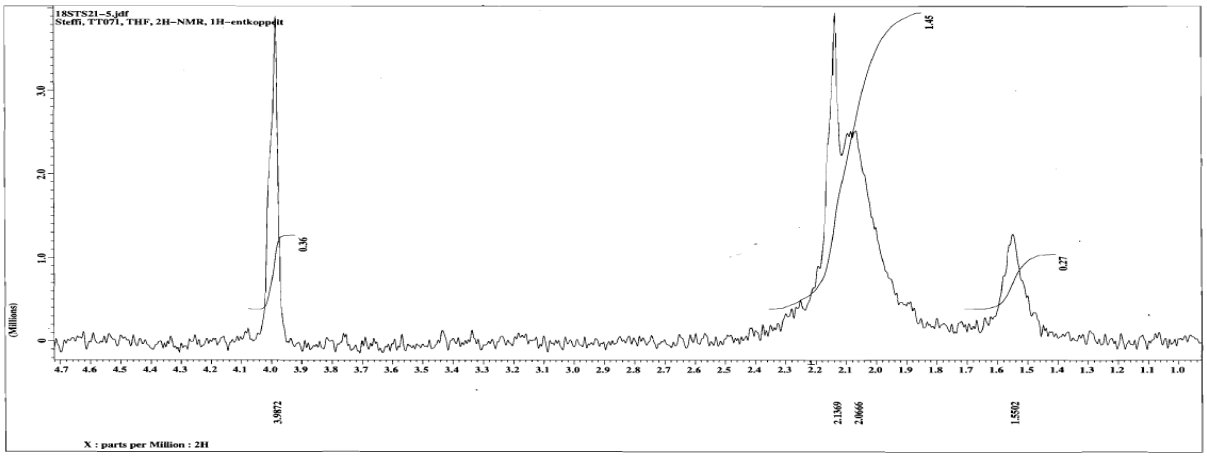
β-cholesteryl deuteride (β-(*eq*)-127)

& α-cholesteryl deuteride (α-(*ax*)-127)



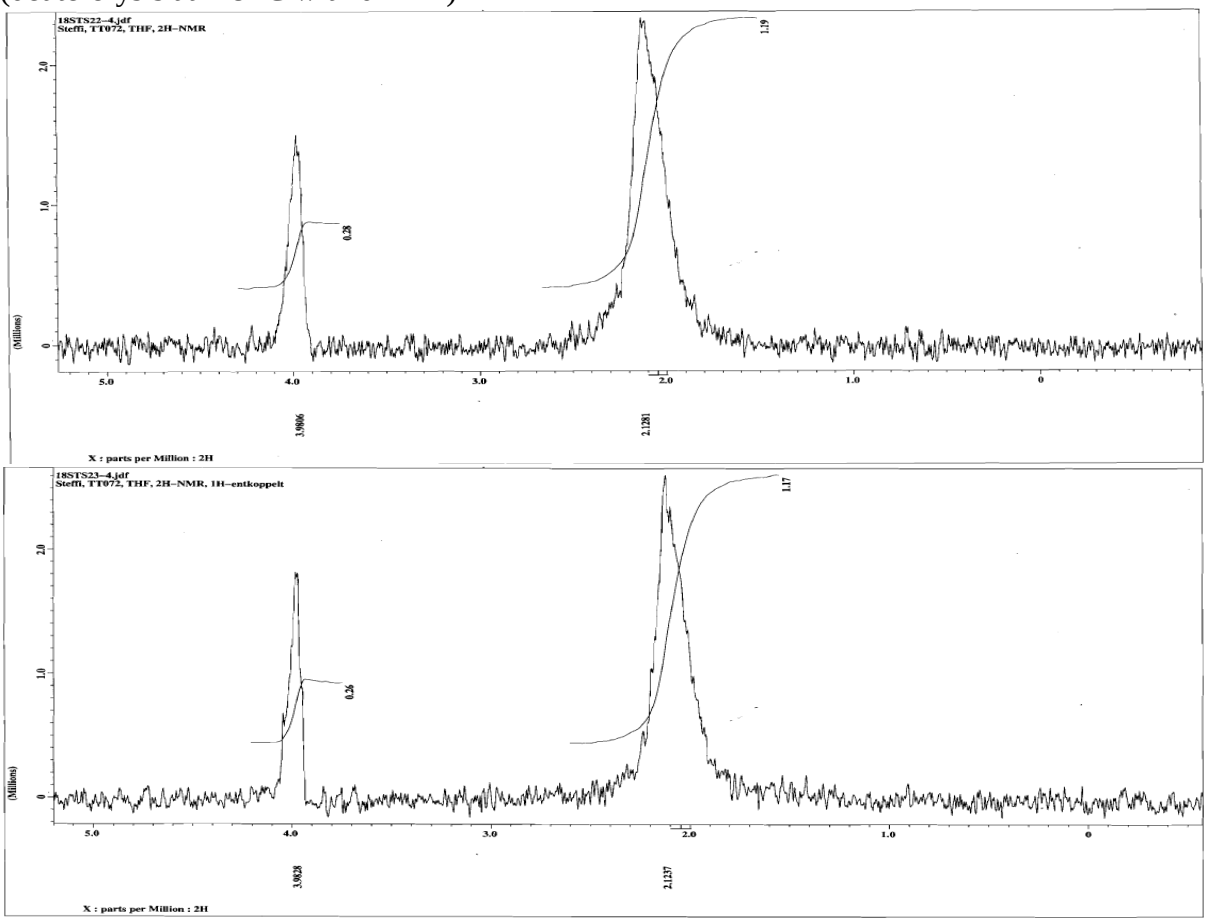
(deuterolysis at rt with d-TFA)





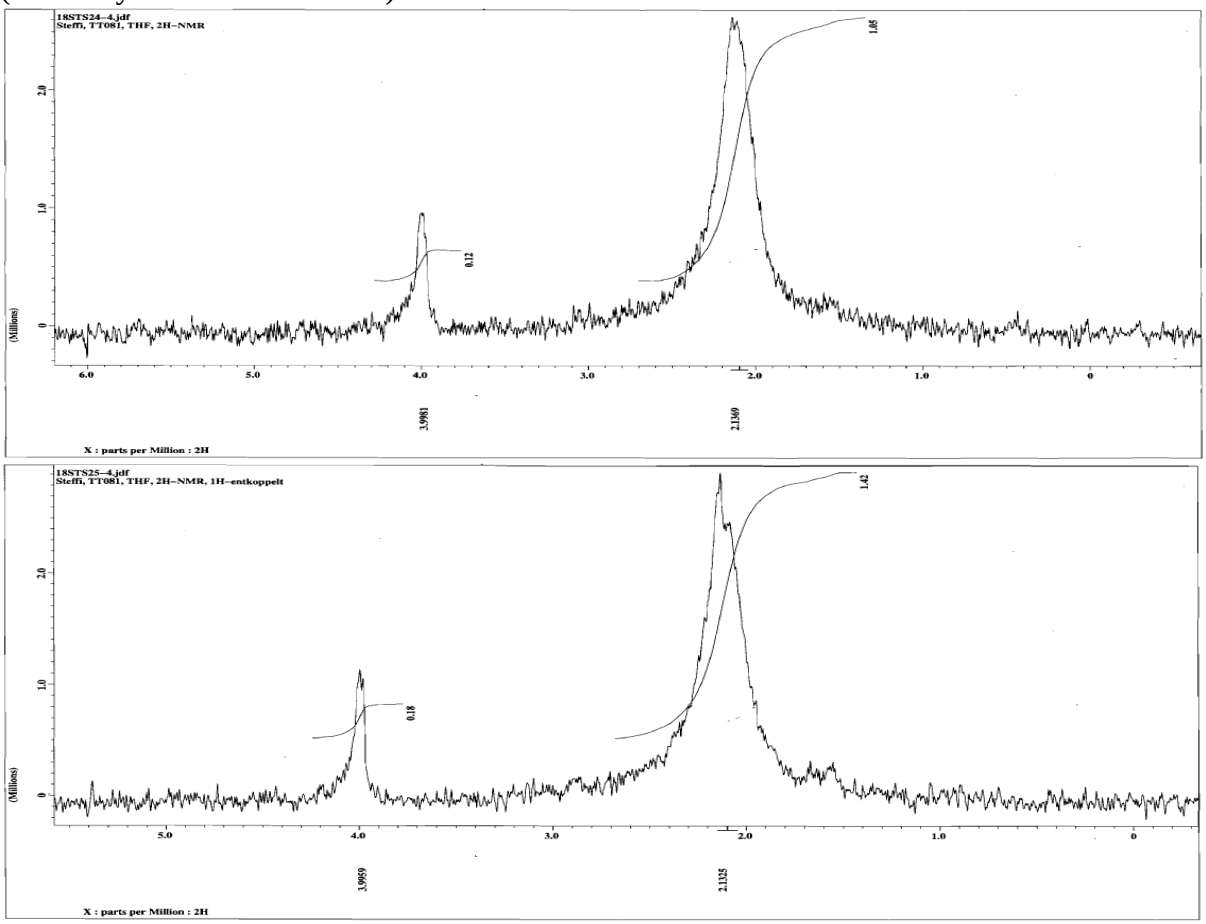
d.r.: 82:18.
^{2}H-NMR (61 MHz, THF) δ: 2.13 (s, 1 D) (major), 1.56 (s, 1 D) (minor).

(deuterolysis at -78 ^{o}C with d-TFA)



d.r.: >99:1.
^{2}H-NMR (61 MHz, THF) δ: 2.13 (s, 1 D).

(deuterolysis at rt with MeOD)

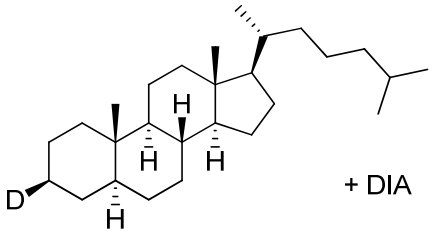


d.r.: >99:1.

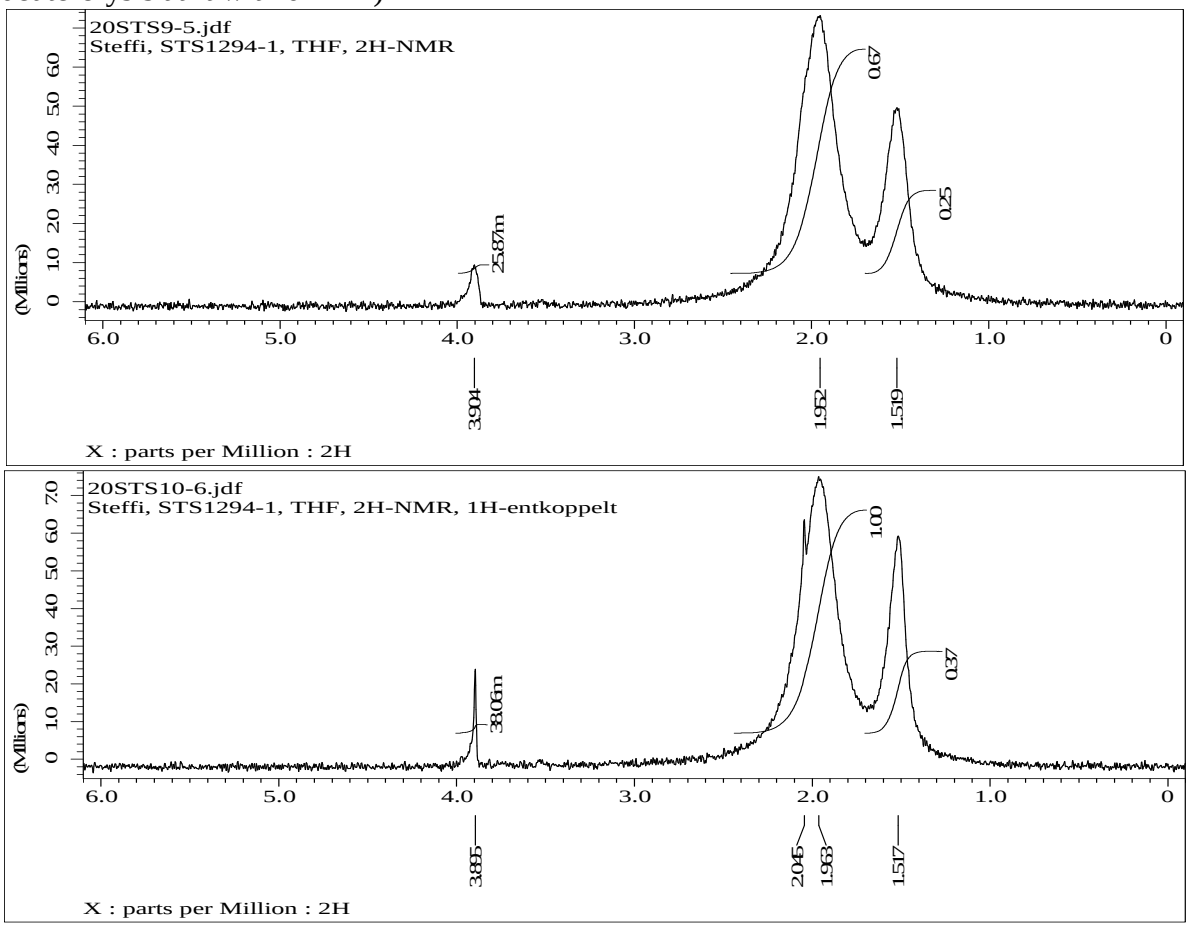
^{2}H-NMR (61 MHz, THF) δ: 2.14 (s, 1 D) (major).

β-cholestanyl deuteride (β-(*eq*)-129)

& α-cholestanyl deuteride (α-(*ax*)-129)



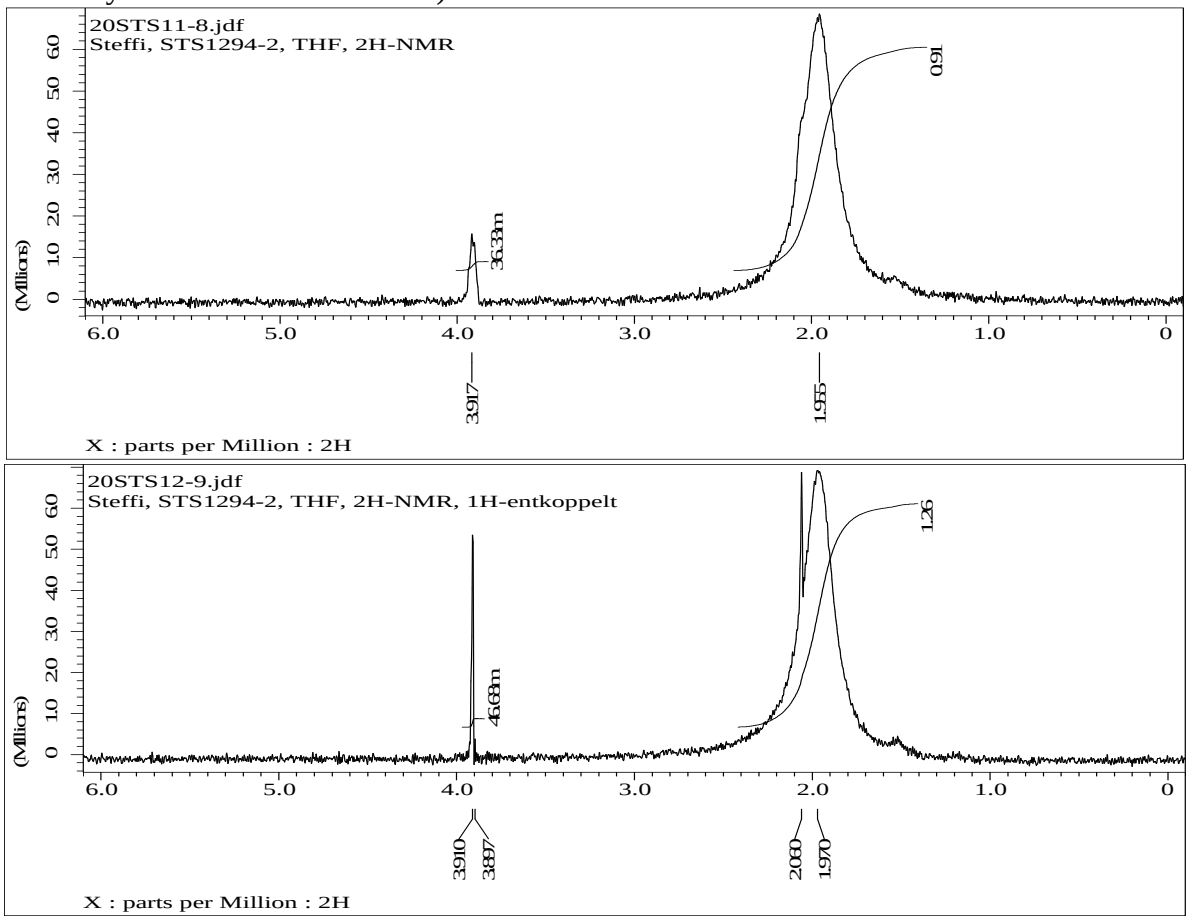
(deuterolysis at rt with d-TFA)



d.r.: 79:21.

^{2}H-NMR (61 MHz, THF) δ: 1.95 (s, 1 D) (major), 1.52 (s, 1 D) (minor).

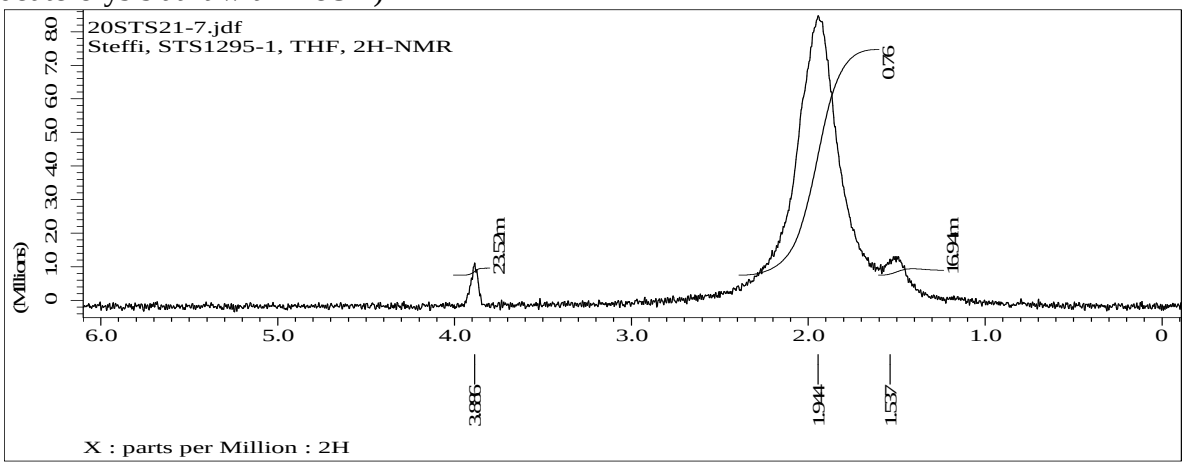
(deuterolysis at -78 °C with d-TFA)

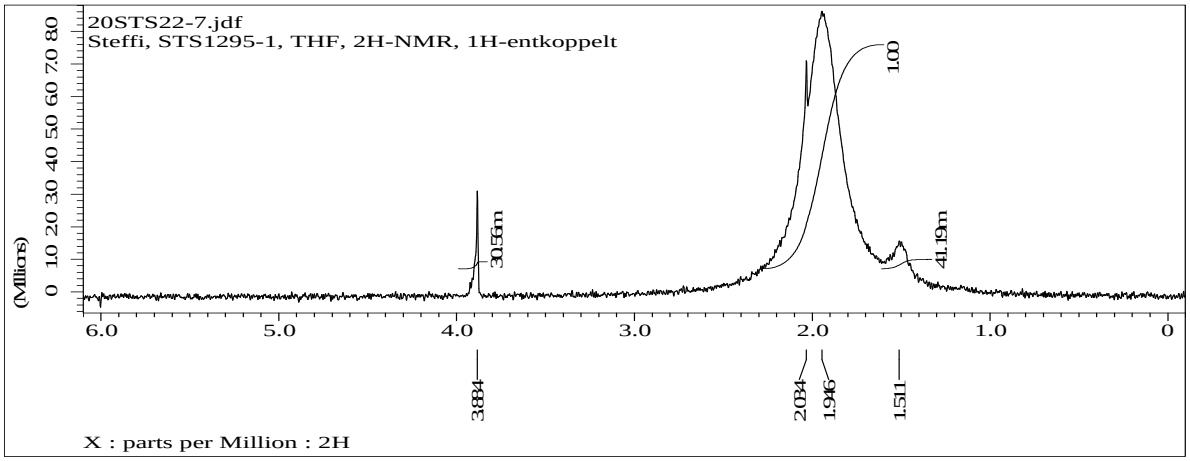


d.r.: 99:1.

^{2}H-NMR (61 MHz, THF) δ: 1.96 (s, 1 D).

(deuterolysis at rt with MeOD)

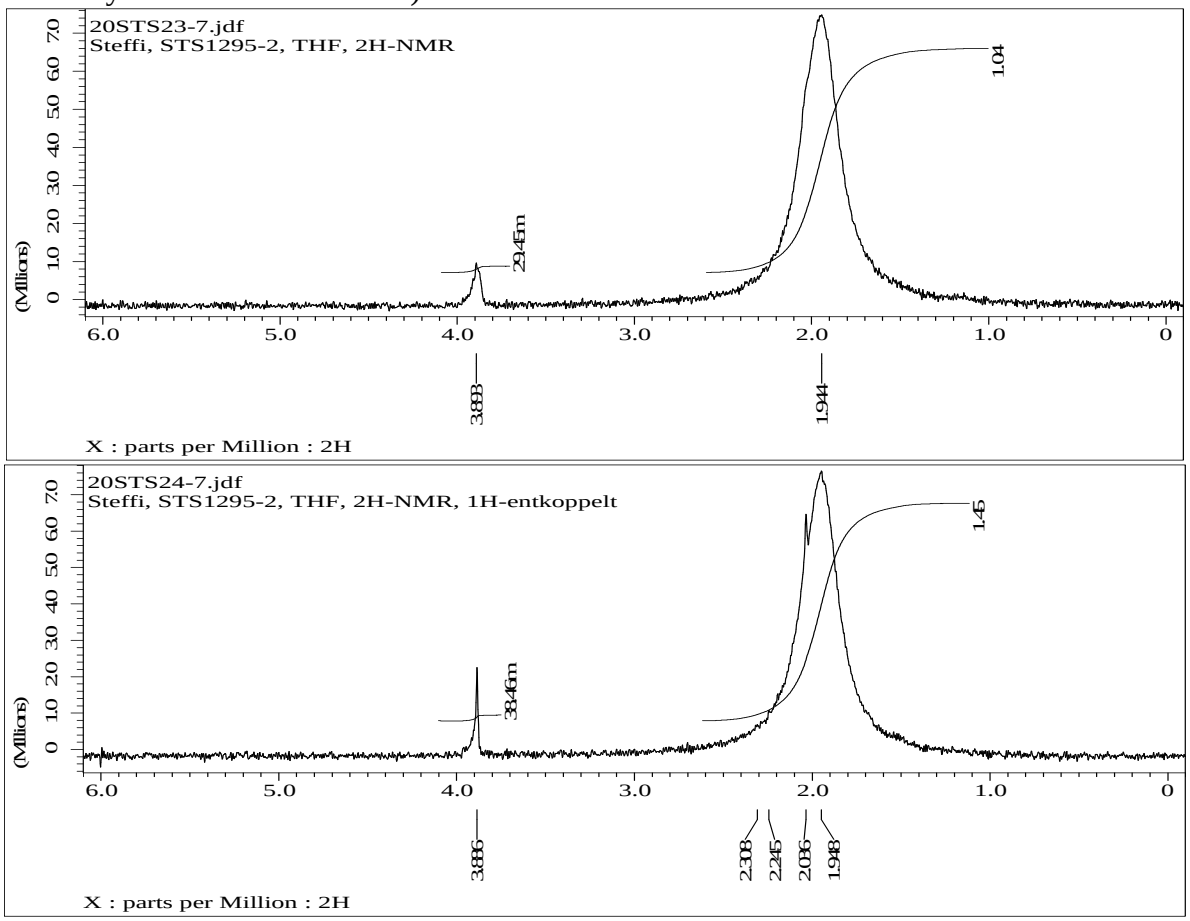




d.r.: 90:10.

^{2}H-NMR (61 MHz, THF) δ: 1.94 (s, 1 D) (major), 1.54 (s, 1 D) (minor).

(deuterolysis at 0 ^{o}C with d-TFA)



d.r.: >99:1.

^{2}H-NMR (61 MHz, THF) δ: 1.94 (s, 1 D).

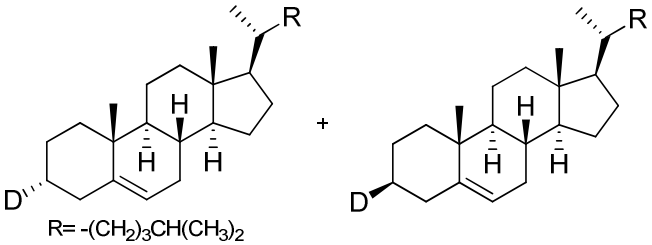
3.1.2. Typical Procedure 4: Protolysis of deuteron-organozinc reagents (TP 4) (Compounds of **Table 5**)

An *in vacuo* dried, Ar-flushed 10 mL *Schlenk*- flask, equipped with a magnetic stirring bar was charged with the respective *α*-deutero-cyclohexylzinc compound (0.25 mmol, 1.0 equiv.). The flask was then cooled to the corresponding temperature, stirred for 10 min at that temperature before TFA (10 equiv.) or MeOH (10 equiv.) were added neat. After 20 min, the reaction was quenched with NH_4Cl sat. solution (2 mL). It was neutralized with $NaHCO_3$ sat. solution. Phases were separated followed by extracting the aqueous phase with 1 mL Et_2O (2 x). The org. phases were combined, dried over Na_2SO_4. The solution was concentrated at the rotary evaporator (careful! Products are volatile!) to 0.6 mL. These were transferred into an NMR tube and analyzed.

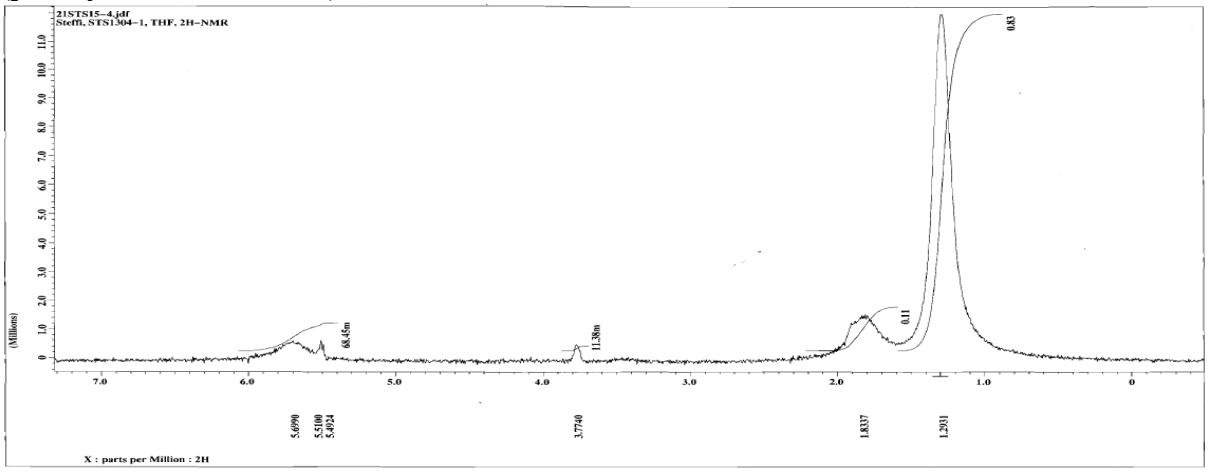
β-cholesteryl deuteride (β-(*eq*)-127)

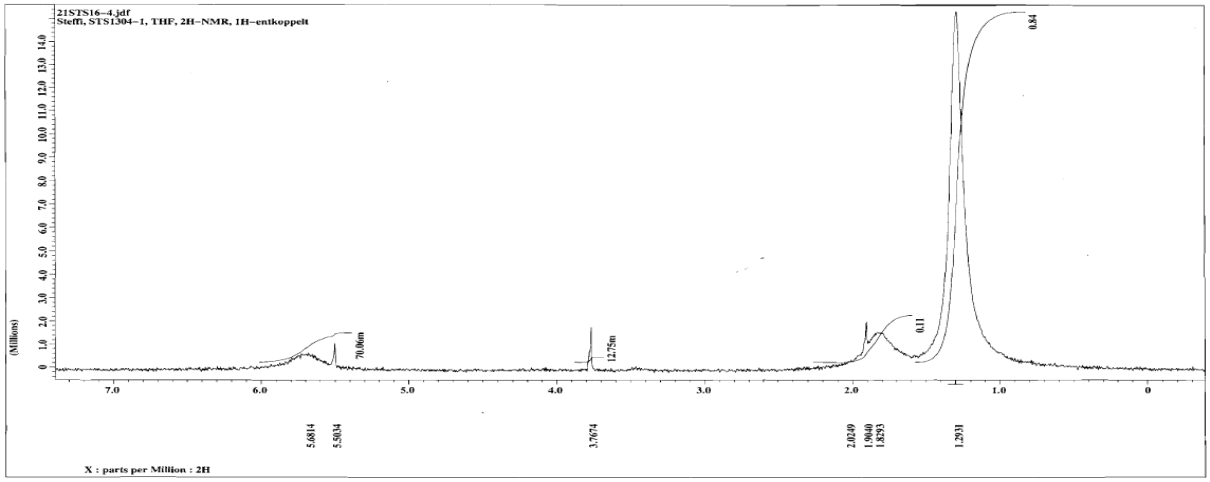
& α-cholesteryl deuteride (α-(*ax*)-127)

from *α-deuterated cholesterylzinc iodide* d-126



(protolysis at rt with TFA)





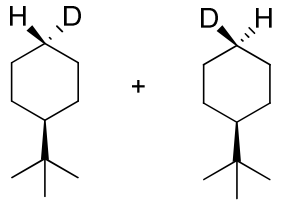
d.r.: 12:88.

^{2}H-NMR (61 MHz, THF) δ: 1.83 (s, 1 D) (minor), 1.29 (s, 1 D) (major).

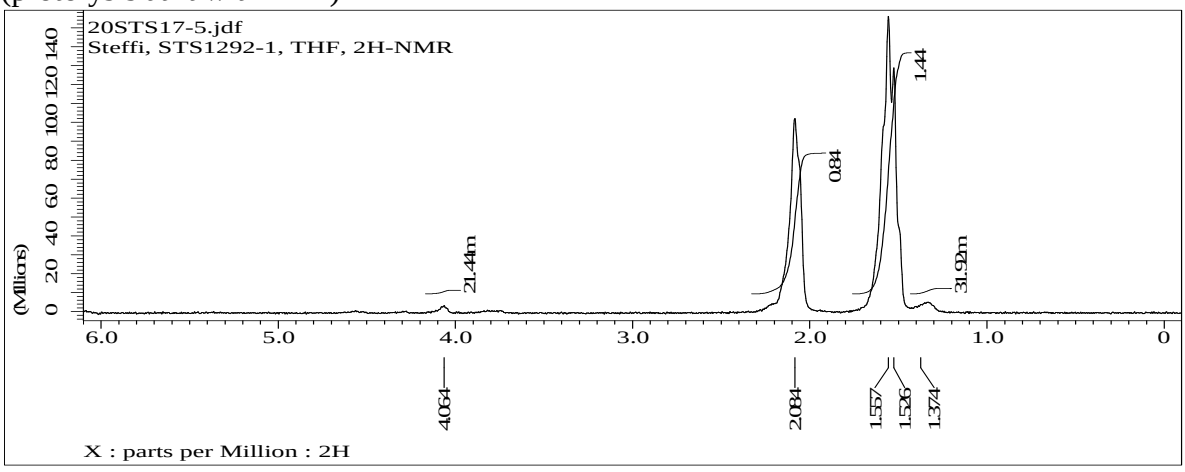
trans-_tert_-butyl(4-$^2H_1$)cyclohexane (_trans_-(_eq_)-117)

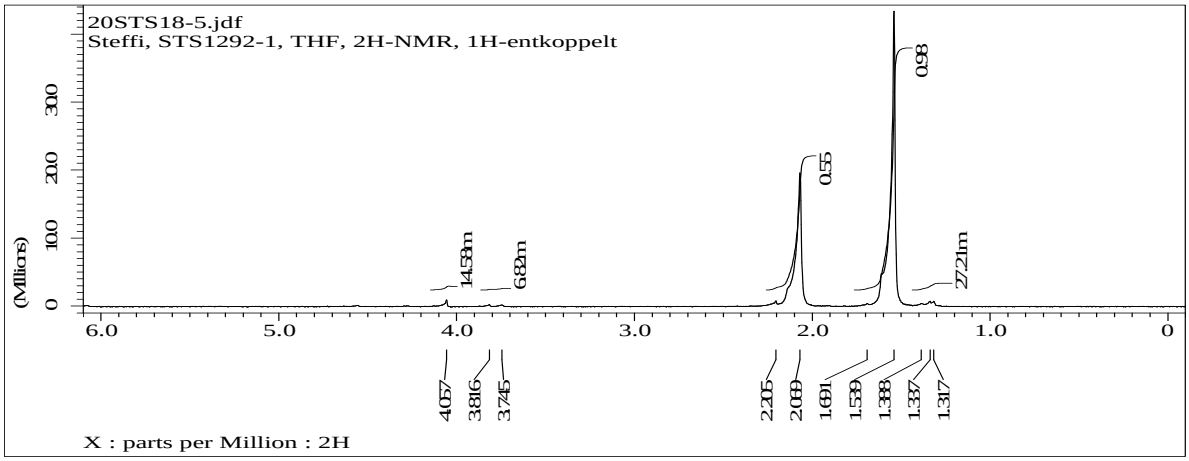
& _cis_-1-(_tert_-butyl)-4-deuterocyclohexane (_cis_-(_eq_)-117)

from _α-deuterated 4-tert-butylcyclohexylzinc iodide_ d-112



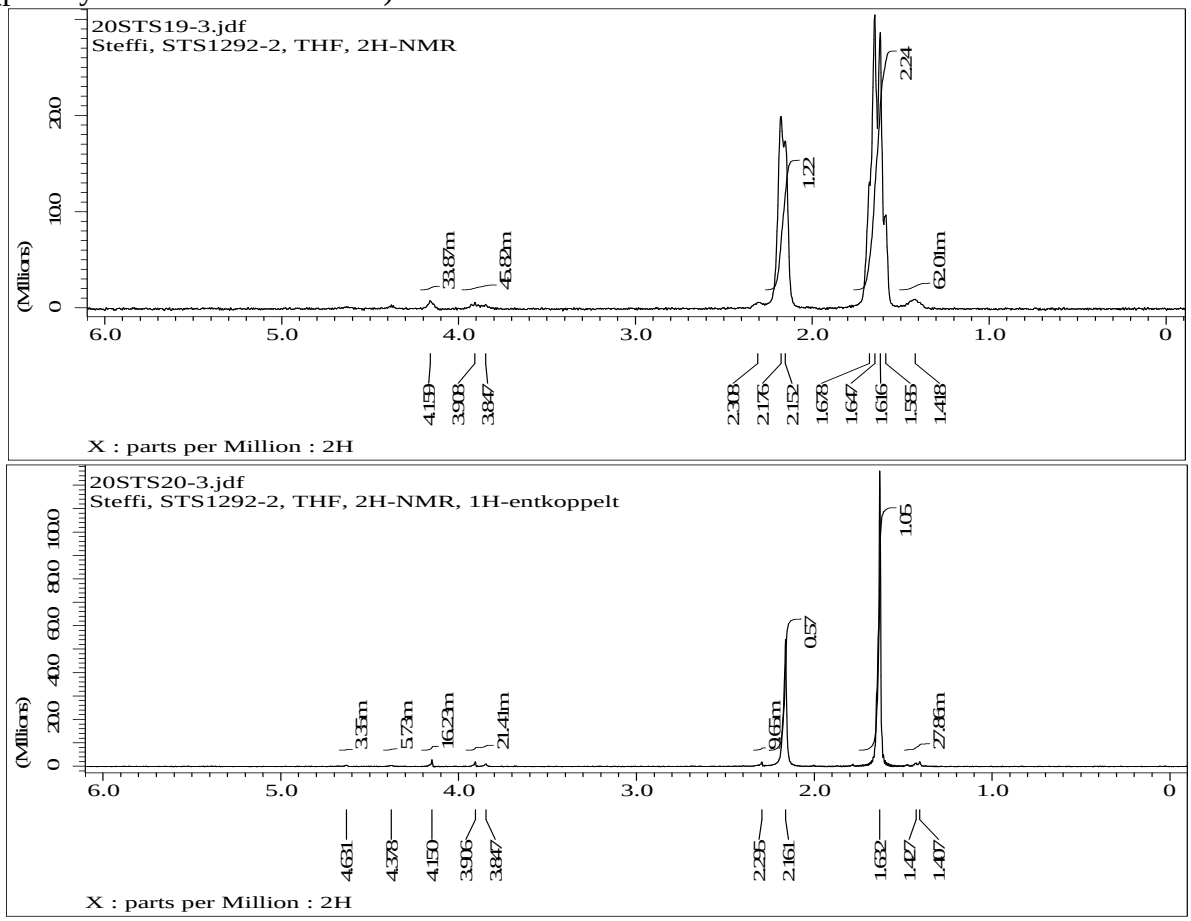
(protolysis at rt with TFA)





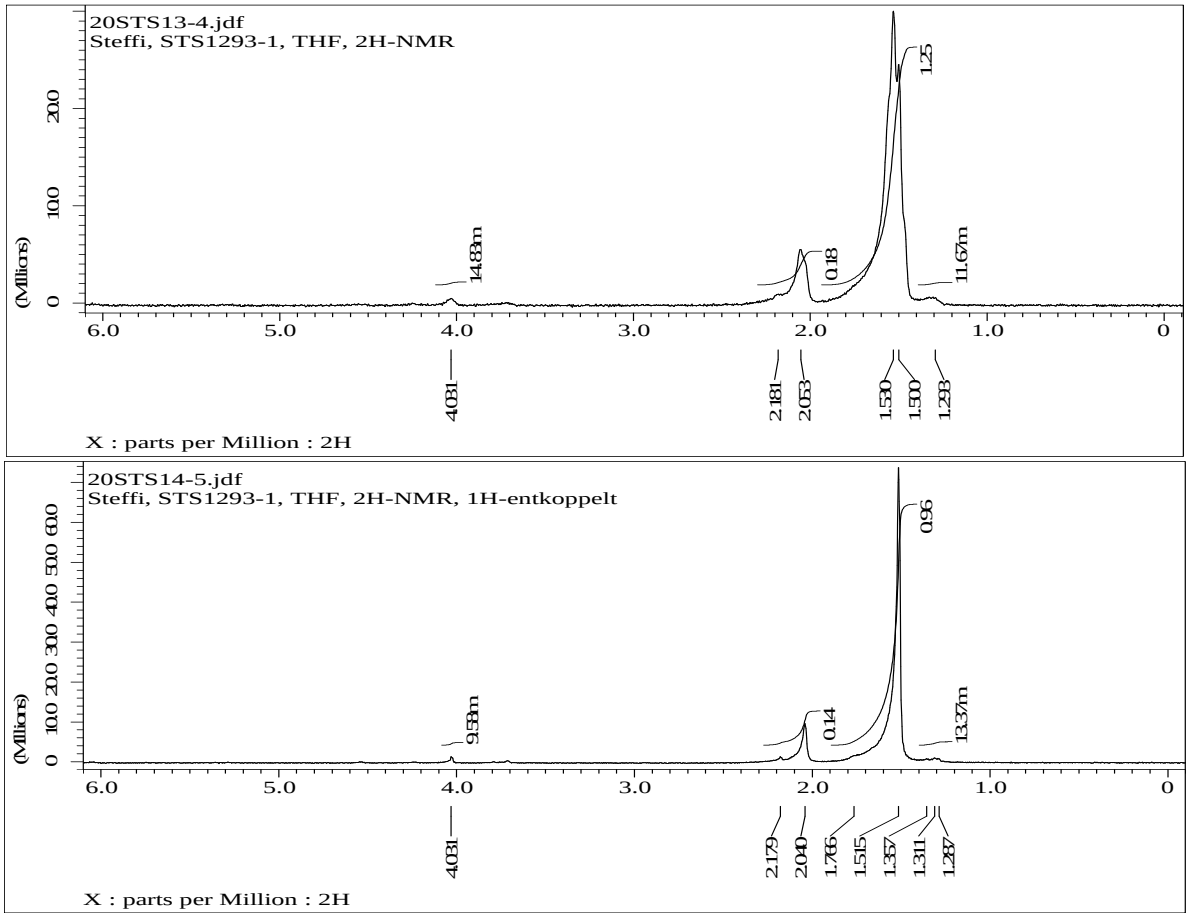
d.r.: 36:64.
^{2}H-NMR (61 MHz, THF) δ: 2.08 (s, 1 D) (minor), 1.54 (s, 1 D) (major).

(protolysis at -78 ^{o}C with TFA)



d.r.: 37:63.
^{2}H-NMR (61 MHz, THF) δ: 2.16 (s, 1 D) (minor), 1.63 (s, 1 D) (major).

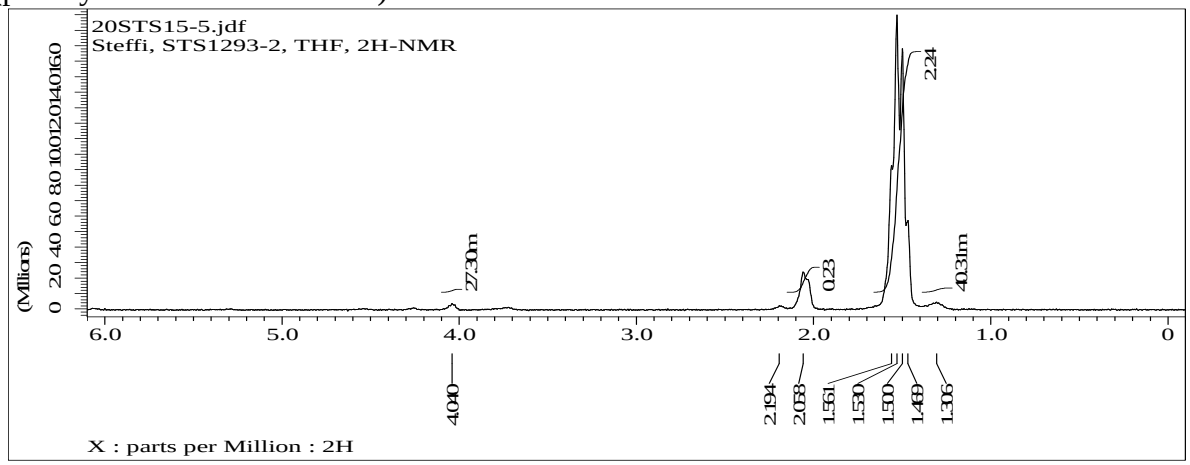
(protolysis at rt with MeOH)

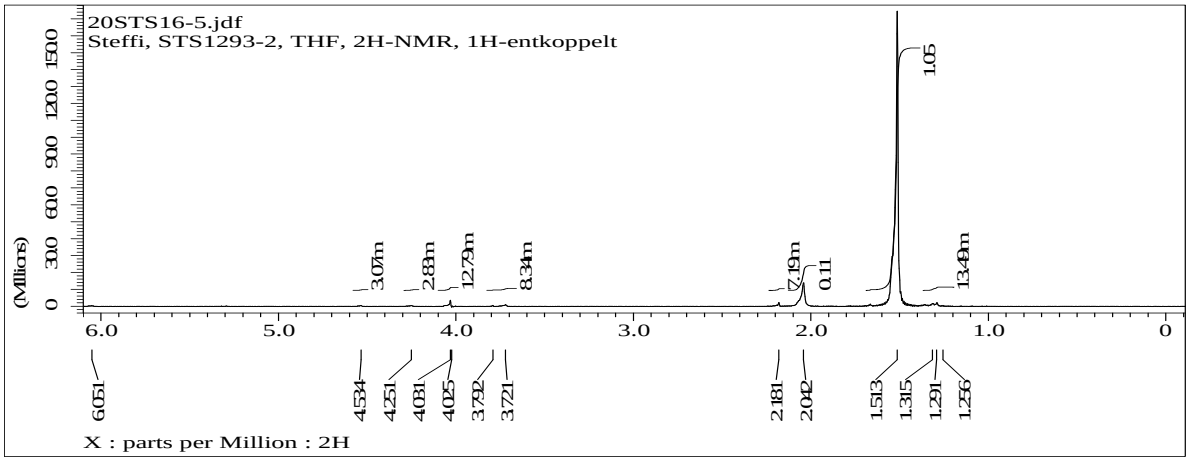


d.r.: 13:87.

^{2}H-NMR (61 MHz, THF) δ: 2.12 (s, 1 D) (minor), 1.52 (s, 1 D) (major).

(protolysis at 0^{o}C with MeOH)





d.r.: 9:91.

^{2}H-NMR (61 MHz, THF) δ: 2.13 (s, 1 D) (minor), 1.52 (s, 1 D) (major).

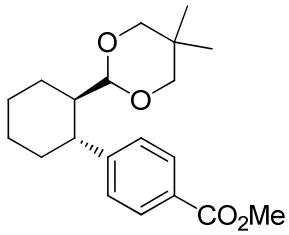
3.2. Cross-Coupling Experiments

3.2.1. Typical Procedure 5: Diastereoselective cross-coupling with stereodefined cyclohexylzinc reagents produced via hydroboration and subsequent boron-zinc exchange (TP5)

(Compounds of **Scheme 31** and **Table 7**)

A dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with the respective cyclohexenyl derivative (1.00 mmol, 1.0 equiv.) in THF (1 mL) and cooled to 0 °C. Et_2BH (0.41 mL, 7.3 M in Me_2S, 3.00 mmol, 3.0 equiv.) was added dropwise, the reaction mixture was allowed to warm up to room temperature and stirred for 48 h at that temperature. After complete hydroboration, the mixture was concentrated (0.1 mm Hg, 25 °C, 2 h) and Et_2Zn (0.31 mL, 3.00 mmol, 3.0 equiv.) was added. After 3 h of stirring, a boron-zinc exchange > 85 % was determined by GC-analysis of an oxidated aliqot (3 M NaOH, 30 % H_2O_2). The reaction mixture was again concentrated (0.1 mm Hg, 25 °C, 1 h), the grey-black residue redissolved in THF (2 mL) and then added dropwise to a mixture of the respective electrophile (3.00 mmol, 3.0 equiv.) $Pd(dba)_2$ (11.5 mg, 0.02 mmol, 2.0 mol%) und S-Phos (8.20 mg, 0.02 mmol, 2.0 mol%) in THF (3 mL) at given temperature. After stirring for the given time and temperature the reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were removed *in vacuo* and the crude product was purified by column chromatography (SiO_2).

methyl-4-(*trans*-2-(5,5-dimethyl-1,3-dioxane-2-yl)cyclohexyl)benzoate (111a)



According to **TP5**, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (**139**) (196 mg, 1.00 mmol) was reacted *via* hydroboration with Et_2BH, followed by a boron-zinc exchange and subsequent cross-coupling (–10 °C, 12 h; then 25 °C 12 h) with methyl-4-iodobenzoate (786 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20 then 1 : 10) furnished the title compound (213 mg, 0.64 mmol, 64 %) as a colourless solid.

d.r.: 98 : 2.

m.p.: 81.4 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.14 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 3.93 (d, J = 2.1 Hz, 1H), 3.47 (s, 3H), 3.32 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 3.25 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 2.83 (d, J = 2.3 Hz, 1H), 2.80 (d, J = 2.3 Hz, 1H), 2.67 (td, J_1 = 11.5 Hz, J_2 = 3.5 Hz, 1H), 2.32-2.36 (m, 1H), 1.83 (tt, J_1 = 11.5 Hz, J_2 = 2.7 Hz, 1H), 1.68-1.78 (m, 2H), 1.57-1.61 (m, 1H), 1.20-1.31 (m, 4H), 1.05 (s, 3H), 0.14 (s, 3H).

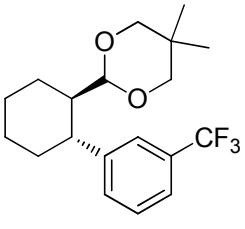
^{13}C-NMR (101 MHz, C_6D_6) δ: 166.7, 151.7, 130.1, 128.9, 101.5, 76.8, 76.8, 51.5, 47.5, 46.0, 35.2, 29.9, 26.9, 26.1, 24.7, 22.9, 21.3.

MS (70 eV, EI) *m/z* (%): 196 (29), 115 (100), 97 (11), 83 (11), 71 (11), 70 (10), 69 (52), 57 (22), 56 (9), 55 (22), 45 (10), 44 (36), 43 (26), 41 (25).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2929 (m), 2852 (m), 1717 (s), 1608 (w), 1438 (m), 1393 (m), 1270 (s), 1184 (m), 1153 (m), 1110 (vs), 1098 (s), 1030 (m), 1017 (m), 987 (m), 973 (m), 932 (m), 852 (w), 770 (s), 710 (s).

HRMS (EI) for **$C_{20}H_{28}O_4$** (332.1988): 332.1977.

2-(*trans*-2-(3-(trifluoromethyl)phenyl)cyclohexyl)–5,5-dimethyl-1,3-dioxane (111b)



According to **TP5**, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (**139**) (196 mg, 1.00 mmol) was reacted *via* hydroboration with Et_2BH, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 1-iodo-3-(trifluoromethyl)benzene (816 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 30) furnished the title compound (232 mg, 0.68 mmol, 68 %) as a colourless oil.

d.r.: 98 : 2.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.53 (s, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.7 Hz, 1H), 3.86 (d, J = 2.2 Hz, 1H), 3.29 (dd, J_1 = 10.8 Hz, J_2 = 2.9 Hz, 1H), 3.21 (dd, J_1 = 10.9 Hz, J_2 = 2.8 Hz, 1H), 2.80 (d, J = 10.8 Hz, 1H), 2.74 (d, J = 11.0 Hz, 1H), 2.62 (td, J_1 = 11.5 Hz, J_2 = 3.1 Hz, 1H), 2.27-2.30 (m, 1H), 1.76 (tt, J_1 = 11.5 Hz, J_2 = 2.8 Hz, 1H), 1.59-1.66 (m, 1H), 1.52-1.57 (m, 2H), 1.11-1.21 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 147.4, 131.1, 130.8 (q, J = 31.7 Hz), 129.0, 125.1 (d, J = 3.4 Hz), 123.1 (q, J = 3.9 Hz) 101.5, 76.8, 76.8, 47.6, 45.7, 35.1, 29.9, 26.9, 26.1, 24.9, 22.9, 21.3.

MS (70 eV, EI) *m/z* (%): 207 (13), 196 (24), 159 (21), 115 (100), 81 (10), 69 (56), 57 (15), 56 (10), 55 (22), 45 (12), 44 (48), 43 (18), 41 (28).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (w), 2853 (w), 1451 (w), 1394 (w), 1328 (s), 1160 (s), 1116 (vs), 1091 (s), 1074 (s), 1042 (m), 1027 (m), 993 (m), 969 (m), 932 (w), 919 (w), 903 (w), 799 (m), 703 (m), 664 (m).

HRMS (EI) for **$C_{19}H_{25}F_3O_2$** (342.1807): 342.1791.

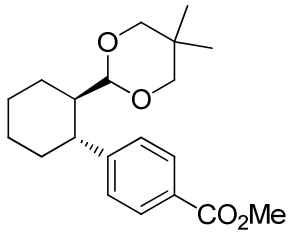
3.2.2. Typical Procedure 6: Diastereoselective cross-coupling with non-stereodefined cyclohexylzinc iodides produced via zinc insertion into the respective cyclohexyl iodide (TP6)

(Compounds of **Scheme 31** and **Table 7**)

In a dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, first LiCl (63.6 mg, 1.50 mmol, 1.5 equiv.) then Zn (196 mg, 3.00 mmol, 3.0 equiv.) were dried under high vacuum at 500 °C for 20 min using a heat gun. After activation with 1,2-dibromoethane (5.0 mol%), THF (2 mL) was added and the reaction was initiated by carefully heating to a gentle reflux with a heat gun. Once the gas development had stopped, a solution of the respective iodide (1.00 mmol, 1.0 equiv.) in THF (1 mL) was added dropwise and the reaction mixture was stirred for 4 h at room temperature. After completion of the zinc

insertion, the reaction mixture was added dropwise to a mixture of the respective electrophile (0.70 mmol, 0.7 equiv.), $Pd(dba)_2$ (11.5 mg, 0.02 mmol, 2.0 mol%) und S-Phos (8.20 mg, 0.02 mmol, 2.0 mol%) in THF (1 mL) at the given temperature. The reaction was stirred for the given time and temperature, then quenched with sat. aq. NH_4Cl solution (10 mL), extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were removed *in vacuo* and the crude product was purified by column chromatography (SiO_2).

methyl-4-(*trans*-2-(5,5-dimethyl-1,3-dioxan-2-yl)cyclohexyl)benzoate



According to **TP6**, 2-(*cis*-2-iodocyclohexyl)-5,5-dimethyl-1,3-dioxane (**148**) (324 mg, 1.00 mmol) was transformed *via* zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (–25 °C, 12 h; then –10 °C, 12 h) with methyl-4-iodobenzoate (183 mg, 0.70 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 10) furnished the title compound (171 mg, 0.51 mmol, 73 %) as a colourless solid.

d.r.: > 99 : 1.

m.p.: 80.4 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.14 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 3.93 (d, J = 2.1 Hz, 1H), 3.47 (s, 3H), 3.32 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 3.25 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 2.83 (d, J = 2.3 Hz, 1H), 2.80 (d, J = 2.3 Hz, 1H), 2.67 (td, J_1 = 11.5 Hz, J_2 = 3.5 Hz, 1H), 2.32-2.36 (m, 1H), 1.83 (tt, J_1 = 11.5 Hz, J_2 = 2.7 Hz, 1H), 1.68-1.78 (m, 2H), 1.57-1.61 (m, 1H), 1.20-1.31 (m, 4H), 1.05 (s, 3H), 0.14 (s, 3H).

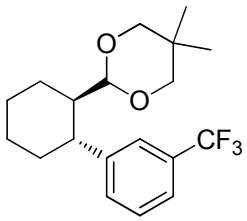
^{13}C-NMR (101 MHz, C_6D_6) δ: 166.7, 151.7, 130.1, 128.9, 101.5, 76.8, 76.8, 51.5, 47.5, 46.0, 35.2, 29.9, 26.9, 26.1, 24.7, 22.9, 21.3.

MS (70 eV, EI) *m/z* (%): 196 (29), 115 (100), 97 (11), 83 (11), 71 (11), 70 (10), 69 (52), 57 (22), 56 (9), 55 (22), 45 (10), 44 (36), 43 (26), 41 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929 (m), 2852 (m), 1717 (s), 1608 (w), 1438 (m), 1393 (m), 1270 (s), 1184 (m), 1153 (m), 1110 (vs), 1098 (s), 1030 (m), 1017 (m), 987 (m), 973 (m), 932 (m), 852 (w), 770 (s), 710 (s).

HRMS (EI) for **$C_{20}H_{28}O_4$** (332.1988): 332.1982.

2-(*trans*-2-(3-(trifluoromethyl)phenyl)cyclohexyl)–5,5-dimethyl-1,3-dioxane



According to **TP6**, 2-(*cis*-2-iodocyclohexyl)-5,5-dimethyl-1,3-dioxane (**148**) (324 mg, 1.00 mmol) was transformed *via* zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (–25 °C, 12 h; then –10 °C, 12 h) with 1-iodo-3-(trifluoromethyl)benzene (190 mg, 0.70 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 30) furnished the title compound (136 mg, 0.40 mmol, 57 %) as a colourless oil.

d.r.: > 99 : 1.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.53 (s, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.7 Hz, 1H), 3.86 (d, J = 2.2 Hz, 1H), 3.29 (dd, J_1 = 10.8 Hz, J_2 = 2.9 Hz, 1H), 3.21 (dd, J_1 = 10.9 Hz, J_2 = 2.8 Hz, 1H), 2.80 (d, J = 10.8 Hz, 1H), 2.74 (d, J = 11.0 Hz, 1H), 2.62 (td, J_1 = 11.5 Hz, J_2 = 3.1 Hz, 1H), 2.27-2.30 (m, 1H), 1.76 (tt, J_1 = 11.5 Hz, J_2 = 2.8 Hz, 1H), 1.59-1.66 (m, 1H), 1.52-1.57 (m, 2H), 1.11-1.21 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 147.4, 131.1, 130.8 (q, J = 31.7 Hz), 129.0, 125.1 (d, J = 3.4 Hz), 123.1 (q, J = 3.9 Hz) 101.5, 76.8, 76.8, 47.6, 45.7, 35.1, 29.9, 26.9, 26.1, 24.9, 22.9, 21.3.

MS (70 eV, EI) *m/z* (%): 207 (13), 196 (24), 159 (21), 115 (100), 81 (10), 69 (56), 57 (15), 56 (10), 55 (22), 45 (12), 44 (48), 43 (18), 41 (28).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (w), 2853 (w), 1451 (w), 1394 (w), 1328 (s), 1160 (s), 1116 (vs), 1091 (s), 1074 (s), 1042 (m), 1027 (m), 993 (m), 969 (m), 932 (w), 919 (w), 903 (w), 799 (m), 703 (m), 664 (m).

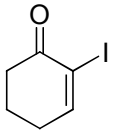
HRMS (EI) for **$C_{19}H_{25}F_3O_2$** (342.1807): 342.1809.

4. Diastereo- and Enantioselective Cross-Coupling with Functionalized Cyclohexylzinc Reagents

4.2. Diastereoselective Cross-Coupling with Functionalized Cyclohexylzinc Derivatives

4.2.1. Preparation of starting materials (Scheme 34)

2-iodocyclohex-2-enone (130)



To a solution of cyclohex-2-enone (50.4 mL, 520 mmol) dissolved in 1.0 L THF/H_2O (1 : 1) was added K_2CO_3 (86.2 g, 624 mmol), I_2 (198 g, 780 mmol) und 4-(dimethylamino)pyridine (DMAP) (12.7 g, 104 mmol). After 2 h of stirring at 25 °C, the reaction mixture was diluted with 250 mL of EtOAc and then cooled to 0 °C. The reaction mixture was then slowly quenched with sat. aq. $NaHSO_3$ solution (400 mL), the organic phase was extracted with 0.1 M HCl solution (2 x 500 mL) and the combined aqueous layers were extracted with EtOAc (3 x 200 mL). The solvent was partly evaporated *in vacuo* (100 mbar, 30 °C) and the residue dissolved in heptane. Crystallisation at -28 °C furnished the title compound (80.1 g, 361 mmol, 69 %) as yellow cristalls.

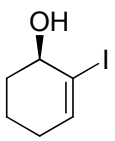
m.p.: 48.4 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.00 (t, J = 4.4 Hz, 1H), 2.03-2.07 (m, 2H), 138-1.43 (m, 2H), 1.15-1.22 (m, 2 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 190.6, 158.6, 104.5, 37.1, 29.4, 22.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2936 (w), 1671 (vs), 1583 (s), 1422 (m), 1408 (m), 1328 (m), 1310 (s), 1155 (m), 1119 (s), 979 (m), 966 (vs), 914 (s), 873 (m), 802 (s), 702 (s).

(*R*)-2-iodocyclohex-2-enol (131)



A dry and argon-flushed 500 mL 2-necked *Schlenk*-flask, equipped with a dropping funnel, a magnetic stirring bar and a septum, was charged with a solution of $B(OMe)_3$ (312 mg,

3.00 mmol) and (*R*)-diphenylprolinol (760 mg, 3.00 mmol) in THF (100 mL) and stirred for 1 h at room temperature. After addition of 2-iodocyclohex-2-enone (**130**) (22.2 g, 100 mmol) the reaction mixture was cooled to 0 °C and borane *N*,*N*-diethylaniline complex (17.9 g, 110 mmol) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for additional 12 h. After addition of sat. aq. $KHSO_4$ solution (200 mL), phases were separated and the aqueous phase was extracted with Et_2O (2 x 200 mL). The combined organic layers were washed with sat. aq. $KHSO_4$ solution, 2 M NaOH solution and sat. aq. NaCl solution and dried over $MgSO_4$. Evaporation of the solvents *in vacuo* (> 200 mbar, 30 °C) furnished the crude product (21.2 g, 94.6 mmol, 95 %), as a pale yellow oil, which was used in the next step without further purification.

^{1}H-NMR (400 MHz, C_6D_6) δ: 6.13 (t, J = 3.9 Hz, 1H), 3.90 (s, 1H), 1.95 (s, 1H), 1.36-1.62 (m, 6H).

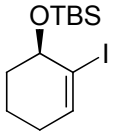
^{13}C-NMR (101 MHz, C_6D_6) δ: 140.5, 104.6, 72.0, 32.3, 29.3, 17.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2936 (m), 2861 (w), 1626 (w), 1426 (m), 1328 (m), 1249 (m), 1161 (m), 1077 (m), 1049 (s), 988 (s), 969 (vs), 931 (m), 903 (m), 869 (m), 827 (m), 803 (s), 773 (m), 738 (s), 690 (m).

4.2.2. Typical Procedure 7: Protection with organosilyl chlorides (TP7)

A dry and Ar-flushed 250 mL *Schlenk-tube*, equipped with a magnetic stirring bar and a septum, was charged with a solution of alcohol (*R*)-2-iodocyclohex-2-enol (**131**) (8.96 g, 40.0 mmol, 1.0 equiv.) and imidazole (6.80 g, 100 mmol, 2.5 equiv.) in DMF (20 mL) at room temperature and the respective organosilyl chloride (50.0 mmol, 1.25 equiv.) was added. After 1 h at 25 °C, the reaction mixture was diluted with Et_2O (150 mL), the organic phase was washed with water (100 mL), 0.5 M HCl solution (120 mL) and sat. aq. NaCl solution (50 mL). The solvents were evaporated *in vacuo* (> 200 mbar, 40 °C) and the crude product was purified *via* column chromatography to give the respective title compound.

(*R*)-*tert*-butyl-(2-iodocyclohex-2-enyloxy)dimethylsilane



According to **TP7**, (*R*)-2-iodocyclohex-2-enol (**131**) (8.96 g, 40.0 mmol) was protected with *tert*-butyldimethylsilylchloride (TBSCl) (7.5 g, 50 mmol). Purification by column

chromatography (SiO_2; Et_2O/*n*-pentane 1 : 50) furnished the title compound (10.4 g, 30.8 mmol, 77 %) as a slightly yellow oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 6.20 (d, J = 3.7 Hz, 1H), 4.08 (s, 1H), 1.57 (d, J = 6.0 Hz, 5H), 1.19-1.24 (m, 1H), 1.03 (s, 9H), 0.27 (s, 3H), 0.06 (s, 3H).

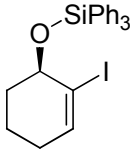
^{13}C-NMR (101 MHz, C_6D_6) δ: 140.3, 103.8, 73.0, 33.7, 29.3, 26.2, 25.9, 18.4, 17.5, -4.0, -4.2.

MS (70 eV, EI) *m/z* (%): 283 (11), 282 (40), 281 (30), 185 (81), 153 (41), 79 (22), 75 (100), 73 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2948 (m), 2928 (m), 2856 (w), 1472 (w), 1360 (w), 1250 (m), 1163 (w), 1088 (s), 1060 (m), 1019 (s), 989 (m), 936 (w), 911 (m), 891 (m), 826 (s), 812 (s), 772 (vs), 712 (m), 695 (w), 667 (m).

HRMS (EI) for **$C_{12}H_{23}IOSi$** (338.0563): 338.0454.

(*R*)-(2-iodocyclohex-2-enyloxy)triphenylsilane



According to **TP7**, (*R*)-2-iodocyclohex-2-enol (**131**) (8.96 g, 40.0 mmol) was protected with triphenylsilylchloride (14.7 g, 50 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 100) furnished the title compound (11.8 g, 24.5 mmol, 61 %) as a colourless solid.

m.p.: 77.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.71-7.75 (m, 6H), 7.36-7.49 (m, 9H), 6.52 (t, J = 3.9 Hz, 1H), 4.33 (t, J = 4.5 Hz, 1H), 2.10-2.20 (m, 1H), 1.72-2.04 (m, 4H), 1.53-1.61 (m, 1H).

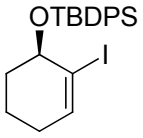
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 141.0, 135.8, 135.6, 135.4, 135.4, 135.2, 134.3, 130.0, 129.8, 127.9, 127.7, 102.2, 73.8, 33.2, 29.4, 17.4.

MS (70 eV, EI) *m/z* (%): 405 (14), 404 (25), 403 (23), 355 (15), 309 (18), 277 (27), 276 (12), 260 (25), 259 (100), 217 (22), 200 (11), 199 (58), 197 (13), 182 (11), 181 (40), 180 (10), 155 (10), 105 (13), 91 (10), 77 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3066 (vw), 2945 (w), 2923 (w), 1589 (vw), 1484 (vw), 1428 (m), 1176 (vw), 1160 (w), 1115 (s), 1094 (s), 1056 (m), 1019 (m), 998 (m), 936 (w), 910 (w), 897 (w), 844 (w), 811 (w), 797 (w), , 739 (m), 705 (s), 697 (vs).

HRMS (EI) for **$C_{24}H_{23}IOSi$** (482.0563): 482.0553.

(*R*)-*tert*-butyl-(2-iodocyclohex-2-enyloxy)diphenylsilane



According to **TP7**, (*R*)-2-iodocyclohex-2-enol (**131**) (8.96 g, 40.0 mmol) was protected with *tert*-butyldiphenylsilylchloride (TBDPSCl) (13.7 g, 50.0 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 50) furnished the title compound (16.1 g, 34.8 mmol, 87 %) as a colourless solid.

m.p.: < 30 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.94-7.96 (m, 2H), 7.84-7.86 (m, 2H), 7.22-7.28 (m, 6H), 6.23 (t, *J* = 3.7 Hz, 1H), 4.28 (d, *J* = 4.4 Hz, 1H), 1.50-1.64 (m, 3H), 1.35-1.43 (m, 2H), 1.28 (s, 9H), 1.02-1.09 (m, 1H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 140.8, 136.8, 136.4, 136.2, 135.9, 135.2, 134.9, 133.6, 130.1, 129.9, 127.9, 127.8, 102.8, 74.1, 33.1, 29.3, 27.5, 19.9, 17.5, 1.4.

MS (70 eV, EI) *m/z* (%): 406 (24), 405 (100), 309 (86), 277 (10), 249 (31), 200 (15), 199 (78), 181 (22), 157 (14), 77 (12).

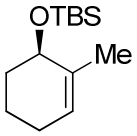
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929 (m), 2856 (m), 1106 (s), 1080 (s), 1056 (s), 1013 (s), 1005 (s), 821 (m), 794.00 (m), 740 (m), 720 (m), 699 (vs), 612(s).

HRMS (EI) for **$C_{22}H_{27}IOSi$** (462.0876): 462.0871.

4.2.3. Typical Procedure 8: Cross-coupling of silyl-protected (*R*)-2-iodocyclohex-2-enol derivatives (TP8) (Schemes 34 and 35)

In a dry and Ar-flushed 25 mL *Schlenk*-flask LiCl (5.0 equiv.) und $ZnCl_2$ (2.5 equiv.) were dried under high vacuum at 500 °C using a heat gun for 20 min. After cooling to room temperature, anhydrous NEP (*N*-ethyl-2-pyrrolidone) (5.5 equiv.) was added and stirring was continued until the salts were dissolved. The solution was cooled to 0 °C, anhydrous THF (0.6 M) was added followed by dropwise addition of the freshly titrated organomagnesium solution (5.0 equiv.). After warming up to room temperature, the aryl iodide (1.0 equiv.) and bis[4-(di-*tert*-butylphosphine)-*N*,*N*-dimethylphenylamino]palladium-dichloride (0.5 mol%) were added and the mixture was heated to 60 °C and left to stir overnight at that temperature. The reaction mixture was then quenched with sat. aq. NH_4Cl solution, extracted with Et_2O and dried over $MgSO_4$. The solvents were removed *in vacuo* and the crude product was subjected to column chromatography.

(*R*)-*tert*-butyldimethyl-(2-methylcyclohex-2-enyloxy)silane (132)



According to **TP8**, LiCl (1.70 g, 40 mmol) und $ZnCl_2$ (2.73 g, 20 mmol) were dried, dissolved in NEP (5.3 mL) and THF (13.3 mL) was added at 0 °C. After complete addition of MeMgCl (20.3 mL, 1.97 M in THF, 40 mmol) at 0 °C the reaction mixture was warmed to room temperature, (*R*)-*tert*-butyl-(2-iodocyclohex-2-enyloxy)dimethyl-silane (2.71 g, 8.00 mmol) and Bis[4-(di-*tert*-butylphosphine)-*N*,*N*-dimethylphenylamino]palladium-dichloride (28.3 mg, 0.04 mmol) were added and the mixture was heated to 60 °C and left to stir overnight at that temperature. Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 50) furnished the title compound (1.48 g, 6.56 mmol, 82 %) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 5.42 (s, 1H), 3.96-3.97 (m, 1H), 1.88-1.92 (m, 1H), 1.77-1.80 (m, 4H), 1.65-1.72 (m, 3H), 1.37-1.44 (m, 1H), 1.00 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

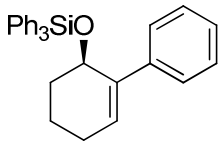
^{13}C-NMR (101 MHz, C_6D_6) δ: 136.4, 124.4, 69.6, 33.4, 26.1, 25.9, 25.8, 21.3, 19.4, 18.3, -4.2, -4.7.

MS (70 eV, EI) *m/z* (%): 226 (12), 169 (49), 93 (37), 77 (10), 75 (100), 73 (11), 41 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2857 (m), 1472 (w), 1462 (w), 1439 (w), 1361 (w), 1250 (m), 1152 (w), 1083 (s), 1072 (s), 1038 (m), 1019 (m), 1003 (s), 963 (w), 939 (w), 893 (s), 832 (vs), 807 (m), 771 (vs), 669 (m).

HRMS (EI) for **$C_{13}H_{26}OSi$** (226.1753): 226.1754.

(*R*)-triphenyl-(2-phenylcyclohex-2-enyloxy)silane



According to **TP8**, LiCl (233 mg, 5.50 mmol) und $ZnCl_2$ (375 mg, 2.75 mmol) were dried, dissolved in NEP (0.7 mL) and THF (1.8 mL) was added at 0 °C. After complete addition of PhMgCl (3.14 mL, 1.75 M in THF, 5.50 mmol) at 0 °C the reaction mixture was warmed to room temperature, (*R*)-(2-iodocyclohex-2-enyloxy)triphenylsilane (531 mg, 1.10 mmol) and Bis[4-(di-*tert*-butylphosphin)-*N*,*N*-dimethylphenylamino]palladium-dichloride (3.54 mg, 0.005 mmol) were added and the mixture was heated to 60 °C and left to stir overnight at that

temperature. Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 100) furnished the title compound (0.39 mg, 0.90 mmol, 82 %) as a colourless solid.

m.p.: 64.6 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.52-7.54 (m, 7H), 7.07-7.20 (m, 13H), 5.89-5.91 (m, 1H), 4.90 (d, J = 4.0 Hz, 1H), 1.85-2.05 (m, 3H), 1.75-1.82 (m, 1H), 1.45-1.53 (m, 1H), 1.32-1.38 (m, 1H).

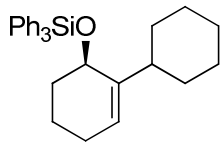
^{13}C-NMR (101 MHz, C_6D_6) δ: 142.0, 140.7, 136.3, 136.0, 135.8, 135.6, 135.5, 135.3, 130.3, 130.3, 130.0, 128.5, 128.4, 127.3, 126.9, 67.9, 32.8, 26.3, 17.9, 1.4.

MS (70 eV, EI) *m/z* (%): 432 (12), 354 (11), 326 (20), 289 (12), 260 (24), 259 (100), 217 (15), 199 (45), 181 (20), 156 (57).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060 (vw), 2933 (w), 1428 (w), 1260 (m), 1114 (s), 1106 (s), 1064 (s), 1013 (s), 800 (s), 739 (m), 705 (s), 695 (vs).

HRMS (EI) for **$C_{30}H_{28}OSi$** (432.1909): 432.1913.

(*R*)-(2-cyclohexylcyclohex-2-enyloxy)triphenylsilane (136)



According to **TP8**, LiCl (1.70 g, 40.0 mmol) und $ZnCl_2$ (2.73 g, 20.0 mmol) were dried, dissolved in NEP (5.3 mL) and THF (13.3 mL) was added at 0 °C. After complete addition of c-HexMgBr (60.6 mL, 0.66 M in THF, 40.0 mmol) at 0 °C the reaction mixture was warmed to room temperature, (*R*)-(2-iodocyclohex-2-enyloxy)triphenylsilane (3.86 g, 8.00 mmol) and Bis[4-(di-*tert*-butylphosphine)-*N*,*N*-dimethylphenylamino]palladium-dichloride (28.3 mg, 0.04 mmol) were added and the mixture was heated to 60 °C and left to stir for 6 h at that temperature. Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1 : 300 then 1 : 200) furnished the title compound (1.66 g, 3.78 mmol, 47 %) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.78-7.84 (m, 6H), 7.20-7.21 (m, 9H), 5.54 (t, J = 3.5 Hz, 1H), 4.50 (d, J = 4.4 Hz, 1H), 2.22 (t, J = 11.2 Hz, 1H), 1.87-2.06 (m, 4H), 1.74-1.84 (m, 2H), 1.54-1.66 (m, 4H), 1.33-1.39 (m, 1H), 1.05-1.27 (m, 4H), 0.85-0.94 (m, 1H).

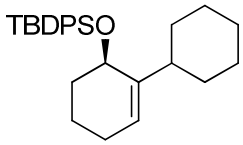
^{13}C-NMR (101 MHz, C_6D_6) δ: 145.2, 136.0, 135.9, 135.8, 135.6, 135.1, 131.0, 130.2, 129.5, 128.1, 127.9, 122.3, 68.6, 40.6, 34.2, 33.1, 32.2, 27.3, 26.9, 25.8, 18.6.

MS (70 eV, EI) *m/z* (%): 438 (12), 356 (20), 355 (68), 260 (20), 259 (100), 199 (39), 181 (10).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2923 (m), 2850 (w), 1428 (m), 1114 (s), 1058 (m), 1029 (m), 1012 (m), 997 (m), 928 (w), 801 (w), 739 (m), 708 (s), 696 (vs).

HRMS (EI) for **$C_{30}H_{34}OSi$** (438.2379): 438.2372.

(*R*)-*tert*-butyl(2-cyclohexylcyclohex-2-enyloxy)diphenylsilane (137)



According to **TP8**, LiCl (1.70 g, 40.0 mmol) und $ZnCl_2$ (2.73 g, 20.0 mmol) were dried, dissolved in NEP (5.3 mL) and THF (13.3 mL) was added at 0 °C. After complete addition of c-HexMgBr (60.6 mL, 0.66 M in THF, 40.0 mmol) at 0 °C the reaction mixture was warmed to room temperature, ((*R*)-*tert*-butyl-(2-iodocyclohex-2-enyloxy)diphenylsilane (3.70 g, 8.00 mmol) and Bis[4-(di-*tert*-butylphosphine)-*N*,*N*-dimethylphenylamino]palladium-dichloride (28.3 mg, 0.04 mmol) were added and the mixture was heated to 60 °C and left to stir for 6 h at that temperature. Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1 : 300 then 1 : 200) furnished the title compound (1.27 g, 3.04 mmol, 38 %) as a colourless solid.

m.p.: < 30 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.82-7.85 (m, 4H), 7.22-7.24 (m, 6H), 5.50 (t, J = 3.5 Hz, 1H), 4.31 (t, J = 4.2 Hz, 1H), 2.15 (t, J = 11.2 Hz, 1H), 2.02 (dd, J_1 = 16.7 Hz, J_2 = 4.4 Hz, 1H), 1.75-1.95 (m, 5H), 1.59 (d, J = 12.7 Hz, 3H), 1.29-1.51 (m, 4H), 1.21 (s, 9H), 1.08-1.12 (m, 2H), 0.77-0.88 (m, 1H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 145.4, 136.4, 135.1, 134.7, 129.8, 127.8, 122.0, 68.2, 40.3, 34.3, 32.9, 31.9, 27.4, 27.3, 26.9, 25.8, 19.7, 18.5.

MS (70 eV, EI) *m/z* (%): 362 (31), 361 (100), 201 (12), 200 (42), 199 (55).

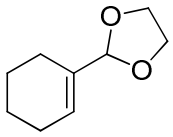
IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2924 (m), 2852 (m), 1427 (w), 1109 (m), 1060 (s), 1021 (s), 822 (m), 738 (m), 699 (vs), 606 (m).

HRMS (EI) for **$C_{28}H_{38}OSi$** (418.2692): 418.2682.

4.2.4. Typical Procedure 9: Protection of cyclohex-2-encarboxaldehyde and acetylcycloalk-2-ene (TP9) (Schemes 37 and 38)

A 250 mL 2-neck flask, equipped with a magnetic stirring bar, a reflux condenser, a *Dean-Stark*-condenser and a drying tube, was charged with the respective *α,β*-unsaturated carbonyl compound (45.4 mmol, 1.0 equiv.), $MgSO_4$ (5.46 g, 45.4 mmol, 1.0 equiv.), L-tartaric acid (41.5 mg, 0.27 mmol, 0.6 mol%) and benzene (60 mL). The respective diol (123 mmol, 2.7 equiv.) was added portionwise at room temperature and the reaction mixture was heated to reflux at 115 °C for 12 h. After cooling to 0 °C, $NaHCO_3$ (45.3 mg, 0.54 mmol, 1.2 mol%) was added as a solid and the reaction mixture was stirred for additional 30 min. The reaction mixture was then filtrated over $NaHCO_3$ and washed with CH_2Cl_2. The solvents were removed *in vacuo* and the crude product was subjected to column chromatography.

2-cyclohex-1-enyl-1,3-dioxolane (138)



According to **TP9**, 1-cyclohexen-1-carboxaldehyde (5.00 g, 45.4 mmol) was protected with 1,2-ethane diole (7.63 g, 6.87 mL, 123 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20) furnished the title compound (6.65 g, 43.1 mmol, 95 %) as a colourless oil.

^{1}H-NMR (300 MHz, C_6D_6) *δ*: 5.88 (m, 1H), 5.15 (s, 1H), 3.39-3.63 (m, 4H), 2.18-2.23 (m, 2H), 1.87 (qd, J_1 = 6.0 Hz, J_2 = 2.5 Hz, 2H), 1.39-1.57 (m, 4H).

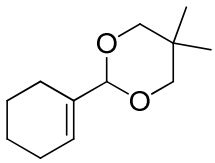
^{13}C-NMR (75 MHz, C_6D_6) *δ*: 135.9, 127.4, 106.9, 65.2, 25.1, 22.8, 22.6, 22.4.

MS (70 eV, EI) *m/z* (%): 154 (92), 153 (95), 126 (18), 125 (100), 99 (11), 43 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928 (m), 2860 (m), 1684 (w), 1438 (w), 1394 (w), 1372 (w), 1300 (w), 1190 (m), 1137 (w), 1093 (s), 1071 (vs), 1042 (s), 943 (s), 837 (s), 801 (m), 690 (m).

HRMS (EI) for **$C_9H_{14}O_2$** (154.0994): 154.0986.

2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (139)



According to **TP9**, 1-cyclohexen-1-carboxaldehyde (5.00 g, 45.4 mmol) was protected with 2,2-dimethylpropane-1,3-diole (12.8 g, 123 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 10) furnished the title compound (8.36 g, 42.6 mmol, 94 %) as a colourless oil.

^{1}H-NMR (300 MHz, C_6D_6) δ: 5.99 (s, 1H), 4.67 (s, 1H), 3.49 (d, J = 10.8 Hz, 2H), 3.21 (d, J = 10.5 Hz, 2H), 2.35-2.40 (m, 2H), 1.92-1.97 (m, 2H), 1.42-1.61 (m, 4H), 1.18 (s, 3H), 0.34 (s, 3H).

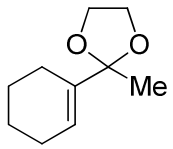
^{13}C-NMR (75 MHz, C_6D_6) δ: 136.5, 125.3, 104.4, 77.2, 30.0, 25.1, 23.6, 23.1, 22.8, 22.7, 21.7.

MS (70 eV, EI) *m/z* (%): 196 (94), 195 (29), 167 (68), 111 (65), 110 (44), 109 (37), 81 (48), 69 (100), 67 (52), 56 (22), 55 (22), 41 (35).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929 (m), 2839 (m), 1470 (w), 1390 (m), 1362 (w), 1184 (m), 1100 (vs), 1015 (m), 979 (s), 911 (m), 838 (m), 801 (w), 644 (w).

HRMS (EI) for **$C_{12}H_{20}O_2$** (196.1463): 196.1461.

2-cyclohex-1-enyl-2-methyl-1,3-dioxolane (149)



According to **TP9**, 1-cyclohexenylethanone (12.4 g, 100 mmol) was protected with 1,2-ethane diol (16.8 g, 15.1 mL, 270 mmol) Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 30) furnished the title compound (10.4 g, 61.8 mmol, 62 %) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 6.02 (dt, J_1 = 3.6 Hz, J_2 = 1.9 Hz, 1H), 3.46-3.61 (m, 4H), 2.09 (qd, J_1 = 4.0, J_2 = 2.0 Hz, 2H), 1.92-1.96 (m, 2H), 1.51-1.57 (m, 5H), 1.41-1.47 (m, 2H).

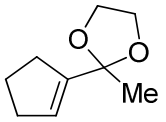
^{13}C-NMR (101 MHz, C_6D_6) δ: 138.6, 122.0, 109,6, 64.3, 25.0, 24.3, 23.1, 22.7.

MS (70 eV, EI) *m/z* (%): 154 (10), 153 (43), 109 (16), 87 (100), 81 (23), 43 (28).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2882 (m), 1668 (w), 1439 (w), 1371 (m), 1273 (w), 1194 (s), 1112 (m), 1076 (m), 1042 (vs), 947 (m), 924 (w), 863 (s), 805 (m).

HRMS (EI) for **$C_{10}H_{16}O_2$** (168.1150): 168.1156.

2-cyclopent-1-enyl-2-methyl-1,3-dioxolane (150)



According to **TP9**, 1-cyclopentenylethanone (5.00 g, 45.4 mmol) was protected with 1,2-ethane diol (7.63 g, 6.87 mL, 123 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20) furnished the title compound (5.63 g, 36.5 mmol, 80 %) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 5.77-5.79 (m, 1H), 3.52-3.62 (m, 4H), 2.37-2.42 (m, 2H), 2.23 (tq, J_1 = 7.4, J_2 = 2.3 Hz, 2H), 1.74-1.82 (m, 2H), 1.57 (s, 3H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 146.1, 126.4, 107.7, 64.7, 32.6, 31.9, 24.4, 24.0.

MS (70 eV, EI) *m/z* (%): 140 (25), 139 (61), 96 (13), 95 (100), 87 (25), 67 (12).

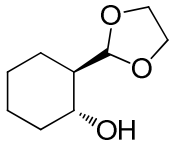
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950 (w), 2886 (w), 2850 (w), 1444 (w), 1371 (m), 1296 (w), 1248 (w), 1184 (s), 1105 (m), 1034 (vs), 947 (m), 863 (s), 811 (m).

HRMS (EI) for **$C_9H_{14}O_2$** (154.0994): 154.1004.

4.2.5. Typical Procedure 10: Preparation of alcohols *via* hydroboration and oxidation (TP10) (Schemes 37 and 38)

A 1.0 M solution of the respective olefin (1.0 equiv.) in THF was placed in a dry and argon-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum. It was cooled to –10 °C and a 1.0 M solution of BH_3·THF-complex (1.1 equiv.) was slowly added. The reaction mixture was then allowed to warm to 0 °C and stirred for 12 h. After completion of the hydroboration a suspension of $NaBO_3$·4 H_2O (13 equiv.) in MeOH/ H_2O (2 : 1) was carefully added. The resulting reaction mixture was stirred for 24 h at room temperature. After filtration, the filtrate was dried over Na_2SO_4 and washed with EtOAc. The solvents were removed *in vacuo* and the crude product was subjected to column chromatography.

***trans*-(1,3-dioxolane-2-yl)cyclohexan-1-ol (145)**



According to **TP10**, 2-cyclohex-1-enyl-1,3-dioxolane (**138**) (2.47 g, 16.0 mmol), dissolved in THF (16 mL) was reacted with BH_3·THF (17.6 mL, 1.0 M in THF, 17.6 mmol). The resulting mixture was then oxidatively quenched with a suspension of $NaBO_3$·$4H_2O$ (32.0 g, 208 mmol)

in MeOH/ H_2O (2 : 1) (96 mL). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 2 : 1 then 3 : 1) furnished the title compound (2.31 g, 13.4 mmol, 67 %) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: = 4.63 (d, J = 5.2 Hz, 1H), 3.73 (s, 1H), 3.67 (td, J_1 = 10.2, J_2 = 4.6 Hz, 1H), 3.33-3.40 (m, 2H), 3.17-3.25 (m, 2H), 2.09-2.16 (m, 1H), 1.81-1.85 (m, 1H), 1.46-1.66 (m, 3H), 1.30-1.40 (m, 1H), 0.95-1.13 (m, 3H).

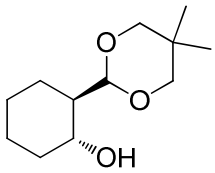
^{13}C-NMR (101 MHz, C_6D_6) δ: 107.6, 70.7, 64.8, 64.2, 48.1, 34.9, 26.4, 25.3, 24.7.

MS (70 eV, EI) *m/z* (%): 171 (2), 154 (2), 125 (2), 91 (7), 82 (6), 81 (3), 74 (4), 73 (100), 67 (4), 57 (2), 45 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2857 (m), 1450 (m), 1402 (m), 1159 (m), 1120 (s), 1063 (vs), 1030 (vs), 981 (s), 944 (s), 847 (m).

HRMS (EI) for **$C_9H_{16}O_3$** (172.1099): 171.1031 (–H).

***trans*-2-(5,5-dimethyl-1,3-dioxane-2-yl)cyclohexan-1-ol (146)**



According to **TP10**, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (**139**) (3.93 g, 20.0 mmol), dissolved in THF (20 mL) was reacted with BH_3·THF (22.0 mL, 1.0 M in THF, 22.0 mmol) The resulting mixture was then oxidatively quenched with a suspension of $NaBO_3$·$4H_2O$ (40.0 g, 260 mmol) in 120 mL MeOH/ H_2O (2 : 1). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 1 then 2 : 1) furnished the title compound (3.06 g, 14.3 mmol, 72 %) as a colourless oil.

^{1}H-NMR (300 MHz, C_6D_6) δ: 4.31 (d, J = 4.1 Hz, 1H), 3.85 (td, J_1 = 10.1 Hz, J_2 = 4.6 Hz, 2H), 3.32 (ddd, J_1 = 11.1 Hz, J_2 = 6.5 Hz, J_3 = 2.8 Hz, 2H), 3.25 (d, J = 6.3 Hz, 1H), 3.02 (dd, J_1 = 11.1 Hz, J_2 = 2.8 Hz, 2H), 2.12-2.18 (m, 1H), 1.81.1.87 (m, 1H), 1.50-1.73 (m, 5H), 1.31-1.45 (m, 1H), 1.06 (s, 3H), 0.25 (s, 3H).

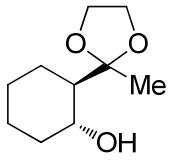
^{13}C-NMR (75 MHz, C_6D_6) δ: 105.3, 77.2, 77.0, 70.8, 48.9, 35.3, 29.9, 26.2, 25.5, 24.8, 22.8, 21.4.

MS (70 eV, EI) *m/z* (%): 127 (29), 115 (100), 83 (33), 81 (35), 71 (20), 69 (80), 67 (21), 57 (47), 56 (23), 55 (56), 44 (23), 43 (49), 41 (51).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2924 (s), 2853 (m), 1450 (m), 1394 (m), 1161 (m), 1116 (vs), 1089 (s), 1042 (s), 1020 (vs), 985 (s), 969 (s), 927 (m), 850 (w).

HRMS (EI) for **$C_{12}H_{22}O_3$** (214.1569): could not be determined via EI-MS.

***trans*-2-(2-methyl-1,3-dioxolane-2-yl)cyclohexan-1-ol (151)**



According to **TP10**, 2-cyclohex-1-enyl-2-methyl-1,3-dioxolane (**149**) (5.05 g, 30.0 mmol) dissolved in THF (30 mL) was reacted with $BH_3 \cdot THF$ (33.0 mL, 1.0 M in THF, 33.0 mmol) The resulting mixture was then oxidatively quenched with a suspension of $NaBO_3 \cdot 4H_2O$ (60.0 g, 390 mmol) in 180 mL MeOH/ H_2O (2 : 1). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 2 : 1) furnished the title compound (2.57 g, 13.8 mmol, 46 %) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 4.50 (s, 1H), 3.62 (td, J_1 = 10.2 Hz, J_2 = 4.6 Hz, 1H), 3.31-3.39 (m, 4H), 2.20-2.26 (m, 1H), 1.86-1.90 (m, 1H), 1.49-1.59 (m, 3H), 1.36-1.46 (m, 1H), 1.20 (s, 3H), 0.90-1.12 (m, 3H).

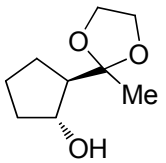
^{13}C-NMR (101 MHz, C_6D_6) δ: 112.9, 71.3, 64.4, 63.7, 51.8, 35.6, 27.2, 26.0, 25.0, 20.1.

MS (70 eV, EI) *m/z* (%): 171 (23), 88 (35), 87 (67), 81 (16), 71 (13), 43 (100), 41 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3508 (w), 2930 (m), 2883 (m), 2858 (m), 1450 (m), 1381 (m), 1220 (m), 1163 (s), 1132 (s), 1101 (s), 1068 (s), 1046 (vs), 1029 (vs), 984 (m), 949 (s), 899 (m), 855 (s).

HRMS (EI) for **$C_{10}H_{18}O_3$** (186.1256): could not be determined via EI-MS.

***trans*-2-(2-methyl-1,3-dioxolane-2-yl)cyclopentan-1-ol (152)**



According to **TP10**, 2-cyclopent-1-enyl-2-methyl-1,3-dioxolane (**150**) (1.54 g, 10.0 mmol) dissolved in THF (10 mL) was reacted with $BH_3 \cdot THF$ (11.0 mL, 1.0 M in THF, 11.0 mmol) The resulting mixture was then oxidatively quenched with a suspension of $NaBO_3 \cdot 4H_2O$ (20.0 g, 130 mmol) in 60 mL MeOH/ H_2O (2 : 1). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 2 : 1 then 3 : 1) furnished the title compound (871 mg, 5.06 mmol, 51 %) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 4.20 (q, J = 7.0 Hz, 1H), 3.43-3.44 (m, 4H), 2.62 (s, 1H), 2.07-2.13 (m, 1H), 1.95 (td, J_1 = 13.0 Hz, J_2 = 7.0 Hz, 1H), 1.66-1.77 (m, 2H), 1.42-1.63 (m, 3H), 1.2 (s, 3H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 111.8, 74.5, 64.7, 64.4, 56.0, 34.8, 26.6, 22.5, 22.3.

MS (70 eV, EI) *m/z* (%): 157 (13), 87 (100), 71 (10), 67 (10), 57 (13), 55 (13), 43 (46), 41 (12).

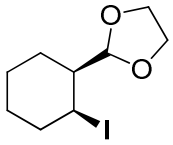
IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2955 (m), 2875 (m), 1448 (w), 1376 (m), 1250 (m), 1222 (m), 1156 (m), 1073 (s), 1030 (vs), 986 (m), 948 (m), 866 (s).

HRMS (EI) for **$C_9H_{16}O_3$** (172.1099): could not be determined via EI-MS.

4.2.6. Typical Procedure 11: Preparation of functionalized cyclohexyl iodides (TP11)

In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, the respective alcohol (0.26 M in THF, 1.0 equiv.) was charged and freshly prepared DCC·MeI (2.0 equiv.) was added at room temperature. The reaction mixture was heated to 50 °C for 24 h. After completion of iodination the reaction mixture was diluted with Et_2O. The layers were separated, the organic phase was extracted with water and the combined aqueous layers were extracted with Et_2O. Then the combined organic layers were washed with sat. aq. $NaHSO_3$ solution and dried over $MgSO_4$. After removal of the solvents *in vacuo* the crude product was subjected to column chromatography.

2-(*cis*-2-iodocyclohexyl)-1,3-dioxolane (147)



According to **TP11**, *trans*-(1,3-dioxolane-2-yl)cyclohexan-1-ol (**145**) (1.03 g, 6.00 mmol) in THF (23 mL) was reacted with DCC·MeI (4.18 g, 12.0 mmol). The reaction mixture was heated to 50 °C for 24 h. Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 30) furnished the title compound (1.06 g, 3.76 mmol, 63 %) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 4.85 (s, 1H), 4.66 (d, J = 7.0 Hz, 1H), 3.39-3.46 (m, 2H), 3.25-3.34 (m, 2H), 1.86-1.94 (m, 2H), 1.69-1.80 (m, 1H), 1.49-1.61 (m, 2H), 1.19-1.27 (m, 2H), 0.96-1.08 (m, 1H), 0.52-0.58 (m, 1H).

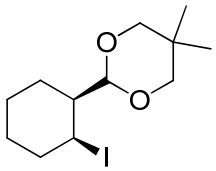
^{13}C-NMR (101 MHz, C_6D_6) δ: 108.9, 64.8, 64.7, 46.9, 39.6, 36.4, 25.2, 24.3, 22.6.

MS (70 eV, EI) *m/z* (%): 154 (100), 93 (13), 83 (11), 73 (63), 45 (13).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2931 (m), 2860 (m), 1446 (m), 1254 (m), 1156 (s), 1130 (m), 1078 (vs), 1059 (s), 1031 (s), 979 (s), 938 (s), 891 (s), 860 (m), 829 (m), 644 (m).

HRMS (EI) for **$C_9H_{15}IO_2$** (282.0117): 282.0092.

2-(*cis*-2-iodocyclohexyl)-5,5-dimethyl-1,3-dioxane (148)



According to **TP11**, *trans*-2-(5,5-dimethyl-1,3-dioxane-2-yl)cyclohexan-1-ol (**146**) (2.57 g, 12.0 mmol) in THF (46 mL) was reacted with DCC·MeI (8.36 g, 24.0 mmol). The reaction mixture was heated to 50 °C for 24 h. Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 30) furnished the title compound (2.31 g, 7.13 mmol, 59 %) as a colourless oil.

^{1}H-NMR (300 MHz, C_6D_6) δ: 4.95 (s, 1H), 4.22 (d, J = 7.5 Hz, 1H), 3.42 (ddd, J_1 = 18.0 Hz, J_2 = 10.9 Hz, J_3 = 2.9 Hz, 2H), 3.23 (d, J = 10.9 Hz, 1H), 3.08 (d, J = 10.9 Hz, 1H), 1.93-1.98 (m, 2H), 1.69-1.84 (m, 1H), 1.48-1.58 (m, 2H), 1.22-1.36 (m, 2H), 1.13 (s, 2H), 1.05 (tt, J_1 = 13.2 Hz, J_2 = 3.7 Hz, 2H), 0.78-0.86 (m, 1H), 0.29 (s, 3H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 106.7, 77.2, 77.1, 46.7, 40.9, 36.4, 30.2, 25.3, 24.0, 23.2, 22.8, 21.5.

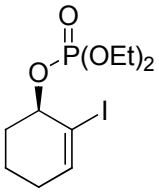
MS (70 eV, EI) *m/z* (%): 197 (46), 115 (64), 111 (25), 97 (34), 83 (100), 71 (26), 69 (96), 67 (36), 57 (54), 56 (31), 55 (86), 41 (35), 39 (50).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928 (s), 2851 (m), 2116 (vs), 1713 (w), 1450 (m), 1391 (m), 1360 (m), 1300 (m), 1257 (w), 1233 (w), 1166 (m), 1150 (m), 1099 (s), 1038 (s), 1022 (s), 993 (m), 976 (s), 948 (m), 892 (m), 864 (m), 834 (w), 786 (m), 645 (m).

HRMS (EI) for **$C_{12}H_{21}IO_2$** (324.0586): 323.0482 [M-H$^-$].

4.3. Synthesis of EOM-Protected Decahydro-1-naphthalinol

(*R*)-diethyl(2-iodocyclohex-2-en-1-yl)phosphate (165) (Scheme 43)



A dry and argon-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with a solution of (*R*)-2-iodocyclohex-2-enole (**131**) (18.7 g, 83.5 mmol) in CH_2Cl_2 (170 mL) and cooled 0 °C. *N*-Methylimidazole (NMI) (13.7 g, 13.3 mL, 167 mmol) was slowly added *via* syringe. After complete addition, the reaction mixture was

stirred for 1 h at that temperature before a solution of diethylchlorophosphate (14.4 g, 12.1 mL, 83.5 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for additional 7 h. The reaction mixture was then quenched with H_2O (150 mL), phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 80 mL). The combined organic layers were washed with sat. aq. NaCl solution (100 mL) and dried over $MgSO_4$. The solvents were evaporated *in vacuo* and the residue was subjected to column chromatography (SiO_2; Et_2O) furnishing the title compound (21.3 g, 59.2 mmol, 71 %) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 6.16 (t, J = 3.7 Hz, 1H), 4.91-4.95 (m, 1H), 4.05-4.14 (m, 2H), 3.84-3.93 (m, 2H), 1.28-1.57 (m, 6H), 1.06-1.11 (m, 3H), 0.96-1.01 (m, 3H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 143.7, 96.2 (d, J = 10.4 Hz), 78.0 (d, J = 4.2 Hz), 64.0 (d, J = 5.4 Hz), 63.5 (d, J = 6.2 Hz), 31.3, 29.0, 16.5, 16.3 (d, J = 6.5 Hz), 16.2 (d, J = 6.9 Hz).

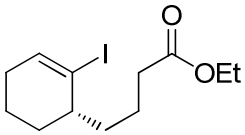
MS (70 eV, EI) *m/z* (%):

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 2935 (w), 1442 (w), 1393 (w), 1368 (w), 1334 (w), 1260 (m), 1164 (w), 1024 (s), 975 (vs), 919 (s), 908 (s), 852 (m), 803 (m), 761 (m), 719 (w), 703 (w).

MS (EI, 70 eV): m/z (%) = 234 (10), 233 (100), 205 (35), 177 (40), 155 (18), 127 (25), 99 (78), 97 (24), 81 (13), 80 (14), 79 (69), 78 (14), 77 (25).

HRMS (EI) for **$C_{10}H_{18}IO_4P$** (359.9987): 359.9973.

(*S*)-ethyl-4-(2-iodocyclohex-2-en-1-yl)butanoate (167)



In a dry and argon-flushed 500 mL *Schlenk*-flask LiCl (10.2 g, 240 mmol) was dried under high vacuum at 500 °C for 20 min. After addition of Zn (39.2 g, 600 mmol) the mixture was dried for additional 30 min at 170 °C under high vacuum and then cooled to room temperature. Anhydrous THF (200 mL) was filled in followed by 1,2-dibromo ethane (1.88 g, 0.87 mL, 10.0 mmol) and trimethylsilylchloride (TMSCl) (4.35 g, 5.06 mL, 40.0 mmol). The reaction was initiated by carefully heating to a gentle reflux using a heat gun and a solution of dry ethyl-4-bromobutyrate (39.0 g, 28.7 mL, 200 mmol) was added dropwise. The reaction mixture was heated to 50 °C and stirred for 12 h. After completion of the zinc insertion the resulting organozinc reagent (106 mL, 0.66 M in THF, 70.0 mmol) was slowly dropped *via* a cannula to a cooled solution of CuCN·2LiCl (70.0 mL, 1.0 M in THF, 70.0 mmol) at –30 °C. After 30 min of stirring a solution of (*R*)-diethyl(2-iodocyclohex-2-en-1-yl)phosphate (**165**)

(12.6 g, 35.0 mmol) in *N*-methylpyrrolidone (63 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for additional 12 h. The reaction mixture was then quenched with sat. aq. NH_4Cl solution (500 mL, mixed with 60 mL 30 % NH_3 solution) and further stirred until all copper salts were dissolved. The phases were separated, the aqueous phase was extracted with Et_2O (3 x 250 mL), the combined organic layers were washed with sat. aq. NaCl solution (250 mL) and dried over $MgSO_4$. The solvents were evaporated *in vacuo* and the residue was subjected to column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20) furnishing the title compound (10.2 g, 31.7 mmol, 91 %) as colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 6.18 (dt, J_1 = 4.1 Hz, J_2 = 1.5 Hz, 1H), 3.95 (q, J = 7.2 Hz, 2H), 2.07 (t, J = 7.5 Hz, 2H), 1.53-1.79 (m, 4H), 1.12-1.46 (m, 7H), 0.97 (t, J = 7.1 Hz, 3H).

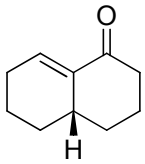
^{13}C-NMR (75 MHz, C_6D_6) δ: 172.7, 138.8, 106.5, 60.0, 45.0, 34.4, 34.3, 29.5, 28.0, 22.5, 18.5, 14.3.

MS (70 eV, EI) *m/z* (%): 195 (65), 150 (25), 149 (77), 132 (10), 131 (57), 121 (33), 107 (100), 105 (12), 93 (19), 91 (24), 81 (12), 80 (18), 79 (63), 77 (21), 67 (18), 41 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2934 (m), 2860 (w), 1731 (vs), 1445 (w), 1373 (m), 1300 (w), 1243 (m), 1176 (s), 1138 (m), 1094 (m), 1034 (m), 963 (m), 927 (w), 863 (w), 802 (w), 724 (m).

HRMS (EI) for **$C_{12}H_{19}IO_2$** (322.0430): 322.0448.

3,4,4a,5,6,7-hexahydro-1(2*H*)-naphthalinone (164)



A dry and argon-flushed 1 L Schlenk-flask, equipped with a dropping funnel and a magnetic stirring bar was charged with a solution of (*S*)-ethyl-4-(2-iodocyclohex-2-en-1-yl)butanoate (**167**) (8.05 g, 25.0 mmol) in THF (500 mL) and cooled to –100 °C. Trimethylsilylchloride (TMSCl) (8.15 g, 9.49 mL, 75.0 mmol) was slowly added *via* syringe. After complete addition the reaction mixture was stirred for 30 min at that temperature before a solution of *t*BuLi (34.2 mL, 1.68 M in THF, 57.5 mmol) was added dropwise. After stirring for 12 h at –70 °C, the reaction mixture was allowed to warm to 0 °C and stirred for additional 12 h. The reaction mixture was then quenched with sat. aq. NH_4Cl solution (330 mL), extracted with Et_2O (3 x 250 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were partly evaporated *in vacuo* (> 500 mbar, 40 °C) and the remainder were removed under

high vacuum at 0 °C. Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 6) furnished the title compound (3.40 g, 22.6 mmol, 90 %) as a pale yellow oil.

^{1}H-NMR (300 MHz, C_6D_6) δ: 6.78-6.82 (m, 1H), 2.37-2.46 (m, 1H), 1.77-2.02 (m, 4H), 1.36-1.55 (m, 4H), 1.09-1.34 (m, 2H), 0.80-0.96 (m, 2H).

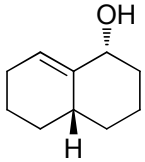
^{13}C-NMR (75 MHz, C_6D_6) δ: 198.2, 139.9, 134.7, 40.2, 37.9, 31.7, 30.6, 26.1, 22.7, 21.8.

MS (70 eV, EI) *m/z* (%): 150 (68), 135 (11), 132 (21), 122 (34), 104 (17), 94 (67), 93 (22), 91 (21), 81 (10), 80 (16), 79 (100), 77 (20), 42 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2925 (m), 2859 (m), 1684 (vs), 1614 (vs), 1452 (m), 1412 (w), 1352 (w), 1320 (w), 1262 (s), 1214 (s), 1180 (m), 1154 (w), 1123 (m), 1082 (w), 1036 (w), 1012 (w), 998 (w), 970 (w), 926 (m), 903 (w), 885 (m), 862 (w), 835 (m), 798 (m), 720 (w), 643 (m).

HRMS (EI) for **$C_{10}H_{14}O$** (150.1045): 150.1036.

1,2,3,4,4a,5,6,7-Octahydro-1-naphthalinol (168)



3,4,4a,5,6,7-hexahydro-1(2*H*)-naphthalinone (**164**) (3.15 g, 21.0 mmol) was added to a solution of $CeCl_3 \cdot 7H_2O$ (52.5 mL, 0.4 M in MeOH, 21.0 mmol) at 25 °C, followed by portionswise addition of $NaBH_4$ (794 mg, 21.0 mmol). The reaction mixture was stirred for 30 min and then quenched with sat. aq. NH_4Cl solution (100 mL). Phases were separated, the aqueous phase was extracted with Et_2O (3 x 180 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* (> 200 mbar, 40 °C) furnished the title compound (2.88 g, 18.9 mmol, 90 %) as a colourless oil, which was used in the next step without further purification.

^{1}H-NMR (300 MHz, C_6D_6) δ: 5.77-5.81 (m, 1H), 3.71-3.77 (m, 1H), 1.88-1.98 (m, 3H), 1.63-1.77 (m, 2H), 1.31-1.58 (m, 4H), 1.06-1.22 (m, 2H), 0.85-0.98 (m, 2H).

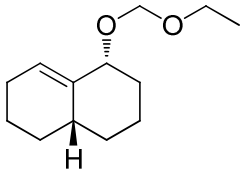
^{13}C-NMR (75 MHz, C_6D_6) δ: 143.1, 116.1, 72.4, 37.6, 36.6, 35.1, 30.9, 25.6, 24.2, 21.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2920 (vs), 2853 (s), 1447 (m), 1354 (m), 1330 (m), 1262 (w), 1138 (m), 1102 (s), 1074 (m), 1058 (s), 1024 (m), 958 (m), 923 (w), 851 (m), 816 (m), 767 (m), 651 (s).

MS (EI, 70 eV): m/z (%) = 152 (82), 134 (31), 124 (46), 123 (100), 119 (21), 110 (87), 109 (51), 97 (25), 95 (21), 93 (33), 92 (25), 91 (49), 81 (52), 79 (60), 77 (22), 67 (36), 41 (20).

HRMS (EI) for **$C_{10}H_{16}O$** (152.1201): 152.1199.

1-(ethoxymethoxy)-1,2,3,4,4a,5,6,7-octahydronaphthaline (169)



In a dry and argon-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum 1,2,3,4,4a,5,6,7-octahydro-1-naphthalinole (**168**) (2.28 g, 15.0 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. After addition of diisopropylethylamine (DIPEA) (3.88 g, 4.96 mL, 30.0 mmol) the reaction mixture was stirred for 30 min at 0 °C before ethoxymethylchlorid (EOMCl) (2.84 g, 2.79 mL, 30.0 mmol) was dropped. The resulting solution was allowed to reach room temperature and stirred for further 12 h. After completion of the reaction sat. aq. NaCl solution (150 mL) was added, the aqueous phase was extracted with Et_2O (3 x 150 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were evaporated *in vacuo* and the residue was subjected to column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 25) furnishing the title compound (3.03 g, 14.4 mmol, 96 %) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 5.94-5.97 (m, 1H), 4.69 (q, J = 7.1 Hz, 2H), 3.90-3.94 (m, 1H), 3.55-3.63 (m, 1H), 3.41-3.49 (m, 1H), 2.02-2.08 (m, 1H), 1.92-1.98 (m, 2H), 1.62-1.75 (m, 2H), 1.46-1.58 (m, 2H), 1.29-1.45 (m, 3H), 1.11-1.24 (m, 3H), 1.07 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 140.7, 116.9, 94.0, 77.4, 63.3, 36.8, 35.2, 35.1, 30.8, 25.6, 24.3, 21.4, 15.4.

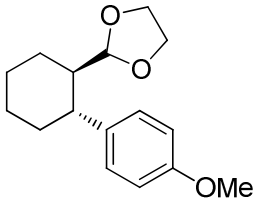
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2974 (w), 2924 (m), 2856 (m), 1447 (w), 1391 (w), 1182 (w), 1134 (m), 1113 (m), 1098 (s), 1037 (vs), 1014 (s), 947 (w), 867 (w), 847 (w), 818 (w), 629 (w).

MS (EI, 70 eV): m/z (%) = 210 (63), 181 (50), 164 (100), 151 (55), 136 (84), 136 (65), 135 (99), 134 (58), 133 (49), 123 (93), 121 (57), 110 (75), 107 (43), 105 (30), 93 (38), 91 (64), 79 (39), 59 (30).

HRMS (EI) for **$C_{13}H_{22}O_2$** (210.1620): 210.1615.

4.4. Diastereoselective Cross-Coupling with Cyclohexylzinc Reagents Produced via Hydroboration and Subsequent Boron-Zinc Exchange (Table 7)

2-(*trans*-2-(4-methoxyphenyl)cyclohexyl)-1,3-dioxolane



According to **TP5**, 2-cyclohex-1-enyl-1,3-dioxolane (**138**) (154 mg, 1.00 mmol) was reacted *via* hydroboration with Et_2BH, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (702 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 10) furnished the title compound (187 mg, 0.71 mmol, 71 %) as a colourless solid.

d.r.: 87 : 13.

m.p.: 52.1 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.07 (d, J = 9.7 Hz, 2H), 6.75 (d, J = 11.0 Hz, 2H), 4.62 (d, J = 5.2 Hz, 1H), 3.37-3.42 (m, 2H), 3.29 (s, 3H), 3.14-3.20 (m, 2H), 2.66 (td, J_1 = 11.7 Hz, J_2 = 3.5 Hz, 1H), 2.09-2.15 (m, 1H), 1.98 (ddt, J_1 = 11.5 Hz, J_2 = 3.5 Hz, J_3 = 1.9 Hz, 1H), 1.62-1.66 (m, 1H), 1.40-1.52 (m, 2H), 1.23-1.32 (m, 4H).

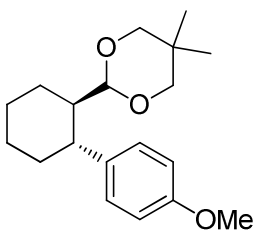
^{13}C-NMR (101 MHz, C_6D_6) δ: 158.6, 137.9, 128.8, 114.2, 104.4, 65.1, 65.0, 54.7, 46.3, 45.9, 36.5, 27.2, 26.1, 24.2.

MS (70 eV, EI) *m/z* (%): 262 [M^+] (25), 201 (13), 200 (48), 154 (69), 125 (12), 121 (24), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2927 (m), 2872 (m), 1609 (m), 1511 (s), 1448 (m), 1306 (w), 1282 (m), 1245 (s), 1177 (s), 1157 (s), 1115 (s), 1097 (m), 1034 (vs), 989 (m), 946 (s), 885 (m), 824 (s), 814 (s), 756 (m), 690 (m).

HRMS (EI) for **$C_{16}H_{22}O_3$** (262.1569): 262.1570.

2-(*trans*-2-(4-methoxyphenyl)cyclohexyl)–5,5-dimethyl-1,3-dioxane



According to **TP5**, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (**139**) (196 mg, 1.00 mmol) was reacted *via* hydroboration with Et_2BH, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (702 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20) furnished the title compound (171 mg, 0.56 mmol, 56 %) as a colourless solid.

d.r.: 98 : 2.

m.p.: 60.7 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.09 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.11 (d, J = 2.1 Hz, 1H), 3.38 (dd, J_1 = 10.7 Hz, J_2 = 2.9 Hz, 1H), 3.31 (s, 3H), 3.28 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 2.92 (d, J = 10.7 Hz, 1H), 2.85 (d, J = 10.7 Hz, 1H), 2.70 (td, J_1 = 11.7 Hz, J_2 = 3.5 Hz, 1H), 2.38-2.42 (m, 1H), 1.89 (tt, J_1 = 11.5 Hz, J_2 = 2.6 Hz, 1H), 1.73-1.81 (m, 2H), 1.64-1.67 (m, 1H), 1.22-1.45 (m, 4H), 1.09 (s, 3H), 0.15 (s, 3H).

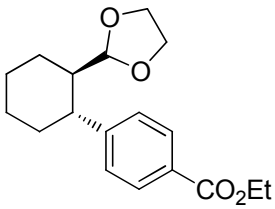
^{13}C-NMR (101 MHz, C_6D_6) δ: 158.6, 138.3, 128.8, 114.2, 101.8, 76.9, 54.7, 48.1, 45.1, 36.0, 30.0, 27.3, 26.4, 24.9, 23.0, 21.4.

MS (70 eV, EI) *m/z* (%): 304 (13), 200 (41), 196 (47), 147 (10), 121 (26), 115 (100), 69 (48).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2923 (s), 2851 (m), 1609 (w), 1512 (s), 1460 (m), 1394 (m), 1284 (m), 1247 (vs), 1176 (m), 1156 (s), 1114 (vs), 1077 (s), 1039 (s), 1026 (s), 989 (s), 967 (s), 822 (s), 814 (s).

HRMS (EI) for **$C_{19}H_{28}O_3$** (304.2038): 304.2041.

ethyl-4-(*trans*-2-(1,3-dioxolane-2-yl)cyclohexyl)benzoate



According to **TP5**, 2-cyclohex-1-enyl-1,3-dioxolane (**138**) (154 mg, 1.00 mmol) was reacted *via* hydroboration with Et_2BH, followed by a boron-zinc exchange and subsequent cross-coupling (–10 °C, 12 h; then 0 °C, 12 h) with ethyl-4-iodobenzoate (828 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 10 then 1 : 1) furnished the title compound (123 mg, 0.71 mmol, 40 %) as a colourless solid.

d.r.: 80 : 20.

m.p.: 69.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.13 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 4.11 (q, J = 7.0 Hz, 2H), 3.33-3.36 (m, 2H), 2.86-2.99 (m, 3H), 2.74-2.78 (m, 1H), 2.23 (td, J_1 = 11.4 Hz,

J_2 = 3.1 Hz, 1H), 1.82-1.87 (m, 1H), 1.64-1.67 (m, 1H), 1.40-1.52 (m, 2H), 1.12-1.26 (m, 4H), 0.99 (t, J = 7.1 Hz, 3H).

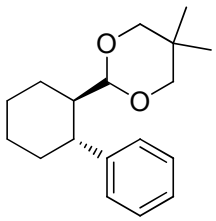
^{13}C-NMR (101 MHz, C_6D_6) δ: 166.3, 151.5, 130.2, 129.8, 129.3, 74.1, 72.3, 61.8, 60.7, 47.1, 43.4, 35.3, 30.5, 26.8, 26.4, 14.3.

MS (70 eV, EI) *m/z* (%): 259 (8), 155 (3), 154 (27), 129 (4), 125 (4), 115 (4), 99 (4), 91 (3), 74 (3), 73 (100), 45 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2856 (m), 1709 (vs), 1608 (m), 1444 (w), 1419 (w), 1366 (w), 1269 (vs), 1182 (m), 1156 (m), 1107 (s), 1094 (vs), 1052 (s), 1040 (m), 1019 (s), 990 (m), 972 (m), 949 (m), 920 (w), 873 (w), 854 (m), 769 (s), 708 (s), 670 (w).

HRMS (EI) for **$C_{18}H_{24}O_4$** (304.1675): 304.1666.

2-(*trans*-2-phenylcyclohexyl)–5,5-dimethyl-1,3-dioxane



According to **TP5**, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (**139**) (196 mg, 1.00 mmol) was reacted *via* hydroboration with Et_2BH, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with iodobenzene (612 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20 then 1 : 10) furnished the title compound (185 mg, 0.67 mmol, 67 %) as a colourless oil.

d.r.: 98 : 2.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.16-7.21 (m, 4H), 7.04-7.09 (m, 1H), 4.06 (d, J = 2.1 Hz, 1H), 3.35 (dd, J_1 = 10.7 Hz, J_2 = 2.9 Hz, 1H), 3.25 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 2.86 (d, J = 10.9 Hz, 1H), 2.79 (d, J = 10.7 Hz, 1H), 2.72 (td, J_1 = 11.8 Hz, J_2 = 3.4 Hz, 1H), 2.37-2.40 (m, 1H), 1.92 (tt, J_1 = 11.4 Hz, J_2 = 2.7 Hz, 1H), 1.72-1.79 (m, 2H), 1.59-1.64 (m, 1H), 1.23-1.44 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 146.4, 128.7, 126.4, 101.6, 76.8, 47.7, 46.0, 35.8, 29.9, 27.2, 26.3, 24.8, 23.0, 21.3.

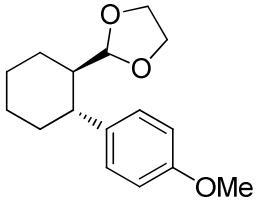
MS (70 eV, EI) *m/z* (%): 273 (13), 196 (72), 170 (13), 167 (15), 159 (10), 117 (15), 116 (21), 115 (100), 91 (51), 69 (90).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (m), 2851 (m), 1451 (m), 1393 (m), 1153 (m), 1115 (vs), 1088 (m), 1078 (m), 1043 (m), 1025 (m), 1017 (m), 991 (m), 967 (m), 931 (m), 756 (s), 699 (vs), 644 (w).

HRMS (EI) for $\mathbf{C_{18}H_{26}O_2}$ (274.1933): 274.1940.

4.5. Diastereoselective Csp^3-Csp^2 Cross-Coupling with Cyclohexylzinc Iodides (Table 8)

2-(*trans*-2-(4-methoxyphenyl)cyclohexyl)-1,3-dioxolane



According to **TP6**, 2-(*cis*-2-iodocyclohexyl)-1,3-dioxolane (**147**) (282 mg, 1.00 mmol) was transformed *via* zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (164 mg, 0.70 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 10) furnished the title compound (81 mg, 0.31 mmol, 44 %) as a colourless solid.

d.r.: 93 : 7.

m.p.: 51.6 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.07 (d, J = 9.7 Hz, 2H), 6.75 (d, J = 11.0 Hz, 2H), 4.62 (d, J = 5.2 Hz, 1H), 3.37-3.42 (m, 2H), 3.29 (s, 3H), 3.14-3.20 (m, 2H), 2.66 (td, J_1 = 11.7 Hz, J_2 = 3.5 Hz, 1H), 2.09-2.15 (m, 1H), 1.98 (ddt, J_1 = 11.5 Hz, J_2 = 3.5 Hz, J_3 = 1.9 Hz, 1H), 1.62-1.66 (m, 1H), 1.40-1.52 (m, 2H), 1.23-1.32 (m, 4H).

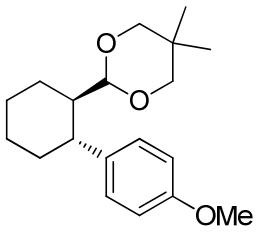
^{13}C-NMR (101 MHz, C_6D_6) δ: 158.6, 137.9, 128.8, 114.2, 104.4, 65.1, 65.0, 54.7, 46.3, 45.9, 36.5, 27.2, 26.1, 24.2.

MS (70 eV, EI) *m/z* (%) :262 [M^+] (25), 201 (13), 200 (48), 154 (69), 125 (12), 121 (24), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2927 (m), 2872 (m), 1609 (m), 1511 (s), 1448 (m), 1306 (w), 1282 (m), 1245 (s), 1177 (s), 1157 (s), 1115 (s), 1097 (m), 1034 (vs), 989 (m), 946 (s), 885 (m), 824 (s), 814 (s), 756 (m), 690 (m).

HRMS (EI) for $\mathbf{C_{16}H_{22}O_3}$ (262.1569): 262.1573.

2-(*trans*-2-(4-methoxyphenyl)cyclohexyl)–5,5-dimethyl-1,3-dioxane



According to **TP6**, 2-(*cis*-2-iodocyclohexyl)-5,5-dimethyl-1,3-dioxane (**148**) (324 mg, 1.00 mmol) was transformed *via* zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (164 mg, 0.70 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20) furnished the title compound (100 mg, 0.33 mmol, 47 %) as a colourless solid.

d.r.: 98 : 2.

m.p.: 56.1 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.09 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.11 (d, J = 2.1 Hz, 1H), 3.38 (dd, J_1 = 10.7 Hz, J_2 = 2.9 Hz, 1H), 3.31 (s, 3H), 3.28 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 2.92 (d, J = 10.7 Hz, 1H), 2.85 (d, J = 10.7 Hz, 1H), 2.70 (td, J_1 = 11.7 Hz, J_2 = 3.5 Hz, 1H), 2.38-2.42 (m, 1H), 1.89 (tt, J_1 = 11.5 Hz, J_2 = 2.6 Hz, 1H), 1.73-1.81 (m, 2H), 1.64-1.67 (m, 1H), 1.22-1.45 (m, 4H), 1.09 (s, 3H), 0.15 (s, 3H).

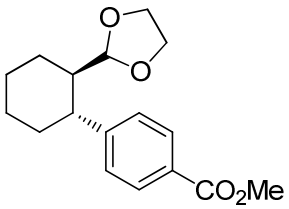
^{13}C-NMR (101 MHz, C_6D_6) δ: 158.6, 138.3, 128.8, 114.2, 101.8, 76.9, 54.7, 48.1, 45.1, 36.0, 30.0, 27.3, 26.4, 24.9, 23.0, 21.4.

MS (70 eV, EI) *m/z* (%): 304 (9), 200 (29), 196 (37), 121 (19), 115 (100), 69 (39).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2927 (m), 2850 (m), 1609 (w), 1511 (s), 1456 (m), 1394 (m), 1363 (w), 1303 (w), 1284 (m), 1246 (vs), 1175 (m), 1154 (s), 1114 (vs), 1076 (m), 1037 (s), 1026 (s), 990 (s), 967 (s), 932 (m), 910 (m), 885 (w), 822 (s), 798 (m), 754 (m), 646 (m).

HRMS (EI) for **$C_{19}H_{28}O_3$** (304.2038): 304.2044.

methyl-4-(*trans*-2-(1,3-dioxolan-2-yl)cyclohexyl)benzoate



According to **TP6**, 2-(*cis*-2-iodocyclohexyl)-1,3-dioxolane (**147**) (282 mg, 1.00 mmol) was transformed *via* zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (–10 °C, 12 h) with methyl-4-iodobenzoate (183 mg, 0.70 mmol).

Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 10 then 1 : 1) furnished the title compound (122 mg, 0.42 mmol, 60 %) as a colourless solid.

d.r.: 81 : 19.

m.p.: 56.9 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.11 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 4.46 (d, J = 1.7 Hz, 1H), 3.49 (s, 3H), 3.27-3.42 (m, 2H), 3.05-3.19 (m, 2H), 2.63 (dt, J_1 = 11.5 Hz, J_2 = 3.6 Hz, 1H), 2.03-2.15 (m, 1H), 1.94 (ddt, J_1 = 11.5 Hz, J_2 = 3.5 Hz, J_3 = 1.9 Hz, 1H), 1.52-1.67 (m, 2H), 1.34-1.47 (m, 1H), 1.12-1.31 (m, 4H).

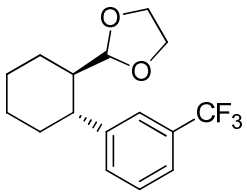
^{13}C-NMR (175 MHz, C_6D_6) δ: 166.7, 151.4, 130.1, 129.7, 128.8, 128.7, 104.4, 64.9, 51.4, 46.6, 45.7, 35.7, 26.9, 25.9, 24.3.

MS (70 eV, EI) *m/z* (%): 259 (3), 154 (22), 149 (3), 129 (3), 115 (3), 99 (3), 74 (3), 73 (100), 45 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2931 (m), 2853 (m), 1712 (vs), 1608 (m), 1573 (w), 1432 (m), 1314 (w), 1272 (vs), 1184 (m), 1155 (m), 1110 (s), 1096 (s), 1053 (m), 1040 (m), 1018 (m), 990 (m), 948 (s), 885 (w), 852 (w), 838 (w), 806 (w), 769 (s), 709 (s), 670 (w).

HRMS (EI) for **$C_{17}H_{22}O_4$** (290.1518): 290.1493.

2-(*trans*-2-(3-(trifluoromethyl)phenyl)cyclohexyl)–1,3-dioxolane



According to **TP6**, 2-(*cis*-2-iodocyclohexyl)-1,3-dioxolane (**147**) (282 mg, 1.00 mmol) was transformed *via* zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (–10 °C, 12 h) with 1-iodo-3-(trifluormethyl)benzene (190 mg, 0.70 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 10) furnished the title compound (166 mg, 0.55 mmol, 79 %) as a colourless oil.

d.r.: 90 : 10.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.52 (s, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.90 (t, J = 7.7 Hz, 1H), 4.35 (d, J = 2.2 Hz, 1H), 3.18-3.36 (m, 2H), 2.97-3.09 (m, 2H), 2.54 (td, J_1 = 11.5 Hz, J_2 = 2.8 Hz, 1H), 1.97-2.02 (m, 1H), 1.83 (ddt, J_1 = 11.5 Hz, J_2 = 3.3 Hz, J_3 = 2.2 Hz, 1H), 1.66-1.70 (m, 1H), 1.48-1.54 (m, 2H), 1.23-1.32 (m, 4H).

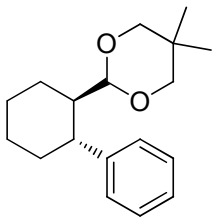
^{13}C-NMR (101 MHz, C_6D_6) δ: 147.2, 131.3, 130.8 (q, J = 31.5 Hz), 129.0, 124.8 (d, J = 3.1 Hz), 123.1 (q, J = 3.9 Hz), 104.3, 65,0, 64.9, 46.4, 45.8, 35.8, 26.8, 25.8, 24.5.

MS (70 eV, EI) *m/z* (%): 300 (17), 299 (28), 281 (37), 185 (10), 165 (10), 159 (35), 154 (26), 129 (10), 73 (100).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2926 (m), 2855 (w), 1450 (w), 1328 (s), 1191 (w), 1159 (s), 1119 (vs), 1089 (m), 1074 (s), 1040 (m), 992 (w), 949 (m), 889 (w), 799 (m), 703 (m), 664 (m).

HRMS (EI) for **$C_{16}H_{19}F_3O_2$** (300.1337): 300.1328.

2-(*trans*-2-phenylcyclohexyl)–5,5-dimethyl-1,3-dioxane



According to **TP6**, 2-(*cis*-2-iodocyclohexyl)-5,5-dimethyl-1,3-dioxane (**148**) (324 mg, 1.00 mmol) was transformed *via* zinc insertion to the corresponding organozinc reagent followed by subsequent cross-coupling (–25 °C, 12 h; then –10 °C, 12 h) with iodobenzene (143 mg, 0.70 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20) furnished the title compound (158 mg, 0.58 mmol, 83 %) as a colourless oil.

d.r.: > 99 : 1.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.16-7.21 (m, 4H), 7.04-7.09 (m, 1H), 4.06 (d, J = 2.1 Hz, 1H), 3.35 (dd, J_1 = 10.7 Hz, J_2 = 2.9 Hz, 1H), 3.25 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 2.86 (d, J = 10.9 Hz, 1H), 2.79 (d, J = 10.7 Hz, 1H), 2.72 (td, J_1 = 11.8 Hz, J_2 = 3.4 Hz, 1H), 2.37-2.40 (m, 1H), 1.92 (tt, J_1 = 11.4 Hz, J_2 = 2.7 Hz, 1H), 1.72-1.79 (m, 2H), 1.59-1.64 (m, 1H), 1.23-1.44 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 146.4, 128.7, 126.4, 101.6, 76.8, 47.7, 46.0, 35.8, 29.9, 27.2, 26.3, 24.8, 23.0, 21.3.

MS (70 eV, EI) *m/z* (%): 273 (13), 196 (72), 170 (13), 167 (15), 159 (10), 117 (15), 116 (21), 115 (100), 91 (51), 69 (90).

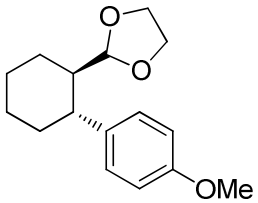
IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2926 (m), 2851 (m), 1451 (m), 1393 (m), 1153 (m), 1115 (vs), 1088 (m), 1078 (m), 1043 (m), 1025 (m), 1017 (m), 991 (m), 967 (m), 931 (m), 756 (s), 699 (vs), 644 (w).

HRMS (EI) for **$C_{18}H_{26}O_2$** (274.1933): 274.1926.

4.6. Typical Procedure 12: Enantioselective Hydroboration/ Boron-Zinc Exchange with Subsequent Cross-Coupling (TP12) (Table 9)

In a dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was placed freshly prepared (–)-IpcBH$_2$ (1.20 mL, 1.0 M in THF, 1.20 mmol, 1.2 equiv.) and cooled to -25 °C. A 1.0 M solution of the respective cyclohexenyl derivative (1.00 mmol, 1.0 equiv.) in THF was added dropwise within 1 h and the resulting mixture was stirred for additional 48 h at that temperature. After complete hydroboration it was allowed to warm to room temperature and concentrated *in vacuo* (0.1 mm Hg, 25 °C, 2 h). Et$_2$BH (0.69 mL, 7.3 M in Me$_2$S, 5.00 mmol, 5.0 equiv.) was added and the mixture was heated to 50 °C for 12 h. The reaction mixture was then concentrated (0.1 mm Hg, 25 °C, 2 h), Et$_2$Zn (0.51 mL 5.00 mmol , 5.0 equiv.) was added dropwise *via* syringe and stirring was continued for 12 h at room temperature. After determination of a boron-zinc exchange > 85 % by GC-analysis of an oxidated aliqot (3 M NaOH, 30 % H_2O_2) the reaction mixture was again concentrated (0.1 mm Hg, 25 °C, 1 h), the grey-black residue redissolved in THF (2 mL) and then added dropwise to a mixture of the respective electrophile (3.00 mmol, 3.0 equiv.) Pd(dba)$_2$ (11.5 mg, 0.02 mmol, 2.0 mol%) und S-Phos (8.20 mg, 0.02 mmol, 2.0 mol%) in THF (3 mL) at the indicated temperature. After stirring for the indicated time and at the indicated temperature, the mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with Et$_2$O (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were removed *in vacuo* and the crude product was purified by column chromatography (SiO_2).

chiral 2-(*trans*-2-(4-methoxyphenyl)cyclohexyl)-1,3-dioxolane



According to **TP12**, 2-cyclohex-1-enyl-1,3-dioxolane (**138**) (154 mg, 1.00 mmol) was reacted *via* asymmetric hydroboration with (–)-IpcBH$_2$, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (702 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et$_2$O/*n*-pentane 1 : 10 then 1 : 1) furnished the title compound (103 mg, 0.39 mmol, 39 %) as a colourless solid.

d.r.: > 99 : 1.

m.p.: 52.0 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.07 (d, J = 9.7 Hz, 2H), 6.75 (d, J = 11.0 Hz, 2H), 4.62 (d, J = 5.2 Hz, 1H), 3.37-3.42 (m, 2H), 3.29 (s, 3H), 3.14-3.20 (m, 2H), 2.66 (td, J_1 = 11.7 Hz, J_2 = 3.5 Hz, 1H), 2.09-2.15 (m, 1H), 1.98 (ddt, J_1 = 11.5 Hz, J_2 = 3.5 Hz, J_3 = 1.9 Hz, 1H), 1.62-1.66 (m, 1H), 1.40-1.52 (m, 2H), 1.23-1.32 (m, 4H).

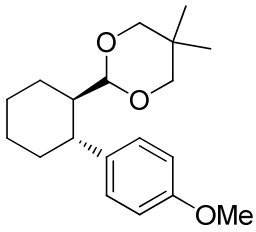
^{13}C-NMR (101 MHz, C_6D_6) δ: 158.6, 137.9, 128.8, 114.2, 104.4, 65.1, 65.0, 54.7, 46.3, 45.9, 36.5, 27.2, 26.1, 24.2.

MS (70 eV, EI) *m/z* (%): 262 [M^+] (25), 201 (13), 200 (48), 154 (69), 125 (12), 121 (24), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2927 (m), 2872 (m), 1609 (m), 1511 (s), 1448 (m), 1306 (w), 1282 (m), 1245 (s), 1177 (s), 1157 (s), 1115 (s), 1097 (m), 1034 (vs), 989 (m), 946 (s), 885 (m), 824 (s), 814 (s), 756 (m), 690 (m).

HRMS (EI) for **$C_{16}H_{22}O_3$** (262.1569): 262.1553.

chiral 2-(*trans*-2-(4-methoxyphenyl)cyclohexyl)–5,5-dimethyl-1,3-dioxane



According to **TP12**, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (**139**) (196 mg, 1.00 mmol) was reacted *via* asymmetric hydroboration with (–)-IpcBH$_2$, followed by a boron-zinc exchange and subsequent cross-coupling (25 °C, 12 h) with 4-iodoanisole (702 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20) furnished the title compound (251 mg, 0.82 mmol, 82 %) as a colourless solid.

d.r.: > 99 : 1.

m.p.: 56.0 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.09 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.11 (d, J = 2.1 Hz, 1H), 3.38 (dd, J_1 = 10.7 Hz, J_2 = 2.9 Hz, 1H), 3.31 (s, 3H), 3.28 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 2.92 (d, J = 10.7 Hz, 1H), 2.85 (d, J = 10.7 Hz, 1H), 2.70 (td, J_1 = 11.7 Hz, J_2 = 3.5 Hz, 1H), 2.38-2.42 (m, 1H), 1.89 (tt, J_1 = 11.5 Hz, J_2 = 2.6 Hz, 1H), 1.73-1.81 (m, 2H), 1.64-1.67 (m, 1H), 1.22-1.45 (m, 4H), 1.09 (s, 3H), 0.15 (s, 3H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 158.6, 138.3, 128.8, 114.2, 101.8, 76.9, 54.7, 48.1, 45.1, 36.0, 30.0, 27.3, 26.4, 24.9, 23.0, 21.4.

MS (70 eV, EI) *m/z* (%): 304 (13), 200 (41), 196 (47), 147 (10), 121 (26), 115 (100), 69 (48).

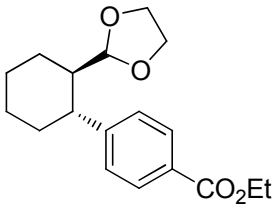
IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2923 (s), 2851 (m), 1609 (w), 1512 (s), 1460 (m), 1394 (m), 1284 (m), 1247 (vs), 1176 (m), 1156 (s), 1114 (vs), 1077 (s), 1039 (s), 1026 (s), 989 (s), 967 (s), 822 (s), 814 (s).

HRMS (EI) for **$C_{19}H_{28}O_3$** (304.2038): 304.2035.

Enantiomeric purity: 73 % *ee*.

HPLC: Column: AD; *n*-Heptan : *i*PrOH: 100 : 0; flux: 0.2 mL/ min.

chiral ethyl-4-(*trans*-2-(1,3-dioxolan-2-yl)cyclohexyl)benzoate



According to **TP12**, 2-cyclohex-1-enyl-1,3-dioxolane (**138**) (154 mg, 1.00 mmol) was reacted *via* asymmetric hydroboration with (–)-IpcBH$_2$, followed by a boron-zinc exchange and subsequent cross-coupling (–5 °C, 12 h) with ethyl-4-iodobenzoate (828 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 10 then 1 : 1) furnished the title compound (96.0 mg, 0.32 mmol, 32 %) as a colourless oil.

d.r.: > 99 : 1.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.13 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 4.11 (q, J = 7.0 Hz, 2H), 3.33-3.36 (m, 2H), 2.86-2.99 (m, 3H), 2.74-2.78 (m, 1H), 2.23 (td, J_1 = 11.4 Hz, J_2 = 3.1 Hz, 1H), 1.82-1.87 (m, 1H), 1.64-1.67 (m, 1H), 1.40-1.52 (m, 2H), 1.12-1.26 (m, 4H), 0.99 (t, J = 7.1 Hz, 3H).

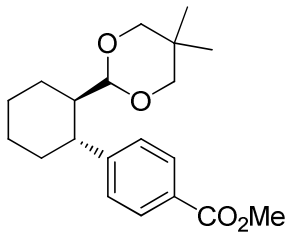
^{13}C-NMR (101 MHz, C_6D_6) δ: 166.3, 151.5, 130.2, 129.8, 129.3, 74.1, 72.3, 61.8, 60.7, 47.1, 43.4, 35.3, 30.5, 26.8, 26.4, 14.3.

MS (70 eV, EI) *m/z* (%):261 (25), 260 (30), 245 (15), 244 (79), 216 (41), 215 (27), 203 (13), 190 (13), 185 (15), 176 (11), 172 (15), 171 (100), 163 (22), 148 (10), 143 (13), 135 (15), 131 (14), 129 (28), 119 (10), 117 (11), 115 (11), 91 (20), 81 (11), 45 (15).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2924 (m), 2854 (m), 1714 (s), 1609 (w), 1448 (w), 1418 (w), 1367 (m), 1311 (w), 1273 (vs), 1179 (m), 1108 (s), 1060 (m), 1020 (m), 848 (w), 708 (m), 771 (m).

HRMS (EI) for **$C_{18}H_{24}O_4$** (304.1675): 305.1753 [M+H$^+$].

chiral methyl-4-(*trans*--2-(5,5-dimethyl-1,3-dioxan-2-yl)cyclohexyl)-benzoate



According to **TP12**, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (**139**) (196 mg, 1.00 mmol) was reacted *via* asymmetric hydroboration with (–)-IpcBH$_2$, followed by a boron-zinc exchange and subsequent cross-coupling (–10 °C, 12 h; then 0 °C, 12 h) with methyl-4-iodobenzoate (786 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20) furnished the title compound (251 mg, 0.82 mmol, 82 %) as a colourless solid.

d.r.: > 99 : 1.

m.p.: 78.6 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.14 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 3.93 (d, J = 2.1 Hz, 1H), 3.47 (s, 3H), 3.32 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 3.25 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 2.83 (d, J = 2.3 Hz, 1H), 2.80 (d, J = 2.3 Hz, 1H), 2.67 (td, J_1 = 11.5 Hz, J_2 = 3.5 Hz, 1H), 2.32-2.36 (m, 1H), 1.83 (tt, J_1 = 11.5 Hz, J_2 = 2.7 Hz, 1H), 1.68-1.78 (m, 2H), 1.57-1.61 (m, 1H), 1.20-1.31 (m, 4H), 1.05 (s, 3H), 0.14 (s, 3H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 166.7, 151.7, 130.1, 128.9, 101.5, 76.8, 76.8, 51.5, 47.5, 46.0, 35.2, 29.9, 26.9, 26.1, 24.7, 22.9, 21.3.

MS (70 eV, EI) *m/z* (%):196 (29), 115 (100), 97 (11), 83 (11), 71 (11), 70 (10), 69 (52), 57 (22), 56 (9), 55 (22), 45 (10), 44 (36), 43 (26), 41 (25).

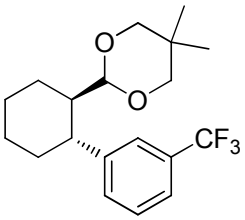
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929 (m), 2852 (m), 1717 (s), 1608 (w), 1438 (m), 1393 (m), 1270 (s), 1184 (m), 1153 (m), 1110 (vs), 1098 (s), 1030 (m), 1017 (m), 987 (m), 973 (m), 932 (m), 852 (w), 770 (s), 710 (s).

HRMS (EI) for **$C_{20}H_{28}O_4$** (332.1988): 332.1980.

Enantiomeric purity: 81 %*ee*.

HPLC: Column: OD; *n*-Heptan : *i*PrOH: 98 : 2; flux: 0.3 mL/min.

chiral 2-(*trans*-2-(3-(trifluormethyl)phenyl)cyclohexyl)–5,5-dimethyl-1,3-dioxane



According to **TP12**, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (**139**) (196 mg, 1.00 mmol) was reacted *via* asymmetric hydroboration with (–)-IpcBH$_2$, followed by a boron-zinc exchange and subsequent cross-coupling (–10 °C, 12 h; then 0 °C, 12 h) with 1-iodo-3-(trifluormethyl)benzene (816 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 30) furnished the title compound (186 mg, 0.54 mmol, 54 %) as a colourless oil.

d.r.: > 99 : 1.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.53 (s, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.7 Hz, 1H), 3.86 (d, J = 2.2 Hz, 1H), 3.29 (dd, J_1 = 10.8 Hz, J_2 = 2.9 Hz, 1H), 3.21 (dd, J_1 = 10.9 Hz, J_2 = 2.8 Hz, 1H), 2.80 (d, J = 10.8 Hz, 1H), 2.74 (d, J = 11.0 Hz, 1H), 2.62 (td, J_1 = 11.5 Hz, J_2 = 3.1 Hz, 1H), 2.27-2.30 (m, 1H), 1.76 (tt, J_1 = 11.5 Hz, J_2 = 2.8 Hz, 1H), 1.59-1.66 (m, 1H), 1.52-1.57 (m, 2H), 1.11-1.21 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 147.4, 131.1, 130.8 (q, J = 31.7 Hz), 129.0, 125.1 (d, J = 3.4 Hz), 123.1 (q, J = 3.9 Hz) 101.5, 76.8, 76.8, 47.6, 45.7, 35.1, 29.9, 26.9, 26.1, 24.9, 22.9, 21.3.

MS (70 eV, EI) *m/z* (%):207 (13), 196 (24), 159 (21), 115 (100), 81 (10), 69 (56), 57 (15), 56 (10), 55 (22), 45 (12), 44 (48), 43 (18), 41 (28).

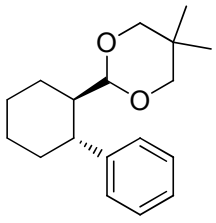
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (w), 2853 (w), 1451 (w), 1394 (w), 1328 (s), 1160 (s), 1116 (vs), 1091 (s), 1074 (s), 1042 (m), 1027 (m), 993 (m), 969 (m), 932 (w), 919 (w), 903 (w), 799 (m), 703 (m), 664 (m).

HRMS (EI) for **$C_{19}H_{25}F_3O_2$** (342.1807): 342.1786.

Enantiomeric purity: 77 % *ee*.

HPLC: Column: OD; *n*-Heptan : *i*PrOH: 100 : 0; flux: 0.2 mL/ min.

chiral 2-(*trans*-2-phenylcyclohexyl)–5,5-dimethyl-1,3-dioxane



According to **TP12**, 2-cyclohex-1-enyl-5,5-dimethyl-1,3-dioxane (**139**) (196 mg, 1.00 mmol) was reacted *via* asymmetric hydroboration with (–)-IpcBH$_2$, followed by a boron-zinc exchange and subsequent cross-coupling (–10 °C, 12 h; then 0 °C, 12 h) with iodobenzene (612 mg, 3.00 mmol). Purification by column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 20) furnished the title compound (143 mg, 0.52 mmol, 52 %) as a colourless oil.

d.r.: >99:1.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.16-7.21 (m, 4H), 7.04-7.09 (m, 1H), 4.06 (d, J = 2.1 Hz, 1H), 3.35 (dd, J_1 = 10.7 Hz, J_2 = 2.9 Hz, 1H), 3.25 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 2.86 (d, J = 10.9 Hz, 1H), 2.79 (d, J = 10.7 Hz, 1H), 2.72 (td, J_1 = 11.8 Hz, J_2 = 3.4 Hz, 1H), 2.37-2.40 (m, 1H), 1.92 (tt, J_1 = 11.4 Hz, J_2 = 2.7 Hz, 1H), 1.72-1.79 (m, 2H), 1.59-1.64 (m, 1H), 1.23-1.44 (m, 4H), 1.00 (s, 3H), 0.11 (s, 3H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 146.4, 128.7, 126.4, 101.6, 76.8, 47.7, 46.0, 35.8, 29.9, 27.2, 26.3, 24.8, 23.0, 21.3.

MS (70 eV, EI) *m/z* (%): 273 (13), 196 (72), 170 (13), 167 (15), 159 (10), 117 (15), 116 (21), 115 (100), 91 (51), 69 (90).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926 (m), 2851 (m), 1451 (m), 1393 (m), 1153 (m), 1115 (vs), 1088 (m), 1078 (m), 1043 (m), 1025 (m), 1017 (m), 991 (m), 967 (m), 931 (m), 756 (s), 699 (vs), 644 (w).

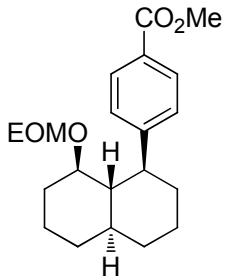
HRMS (EI) for **$C_{18}H_{26}O_2$** (274.1933): 274.1933.

Enantiomeric purity: 68 % *ee*.

HPLC: Column: OD; *n*-Heptan : *i*PrOH: 100 : 0; flux: 0.2 mL/ min.

4.7. Cross-Couplings with [8-(Ethoxymethoxy)decahydronaphthalin-1-yl](ethyl)zinc

4.7.1. Diastereoselective preparation of methyl-4-(8-(ethoxymethoxy)decahydronaphthalin-1-yl)benzoate (Table 10)



A dry and argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with a solution of 1-(ethoxymethoxy)-1,2,3,4,4a,5,6,7-octahydronaphthaline (**169**) (210 mg, 1.00 mmol) in CH_2Cl_2 (2 mL) and freshly prepared Et_2BH (0.41 mL, 7.3 M in Me_2S, 3.00 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 48 h at that temperature. After complete hydroboration the solution was concentrated *in vacuo* (0.1 mm Hg, 25 °C, 2 h), Et_2Zn (371 mg, 0.31 mL,

3.00 mmol) was added and stirring was continued for additional 5 h at room temperature. The reaction mixture was again concentrated (0.1 mm Hg, 25 °C, 1 h), the grey-black residue redissolved in THF (2.5 mL) and then added dropwise to a mixture of methyl-4-iodobenzoate (1.31 g, 5.00 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol) und S-Phos (8.20 mg, 0.02 mmol) in THF (5 mL) at –10 °C. The resulting reaction mixture was left to stir overnight at this temperature before it was quenched with sat. aq. NH_4Cl solution (10 mL). The phases were separated, the aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were evaporated *in vacuo* and the residue was subjected to column chromatography (SiO_2; Et_2O/*n*-pentane 1 : 7) furnishing the title compound (113 mg, 0.31 mmol, 31 %) as a colourless oil.

d.r. (1,2); d.r. (1,3): 91:9; 85:15.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.13 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 3.99 (d, *J* = 7.2 Hz, 1H), 3.60 (d, *J* = 7.2 Hz, 1H) 3.49 (s, 3H), 3.31 (q, *J* = 7.1 Hz, 2H), 1.48-1.60 (m, 4H), 1.08-1.47 (m, 12H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 167.0, 154.8, 129.4, 127.7, 95.9, 83.7, 62.9, 52.1, 51.4, 50.3, 42.0, 38.3, 35.1, 34.1, 34.0, 26.5, 24.3, 15.2.

MS (70 eV, EI) *m/z* (%): 300 (39), 272 (100), 271 (27), 270 (39), 269 (26), 255 (51), 240 (36), 239 (52), 177 (26), 162 (58), 150 (24), 149 (29), 131 (23), 59 (70).

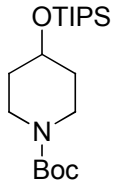
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2924 (m), 2857 (m), 1721 (s), 1609 (m), 1434 (m), 1277 (vs), 1179 (m), 1109 (s), 1099 (s), 1044 (vs), 1017 (s), 847 (m), 771 (m), 708 (m).

HRMS (EI) for **$C_{21}H_{30}O_4$** (346.2144): 346.2135.

5. Highly Diastereoselective Arylations of Substituted Piperidines

5.1. Preparation of Starting Materials

***t*-butyl 4-((triisopropylsilyl)oxy)-piperidine-1-carboxylate (172c)**



To a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (100 mmol; 20.1 g) and imidazole (250 mmol; 17.0 g) in DMF (250 mL) was slowly added TIPSCl (120 mmol; 23.1 g; 25.7 mL) via syringe. The reaction mixture was stirred for further 6 h at room temperature. $NaHCO_3$ sat. aq. solution (500 mL) was added, phases were separated and the aqueous phase was extracted with Et_2O (4 x 300 mL). The combined organic layers were washed with brine (300 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography (SiO_2; *n*-pentane/Et_2O 15:1) yielding 34.1 g (95%) of the title compound.

^{1}H-NMR (400 MHz, C_6D_6) δ: 3.68 (ddd, J_1=10.2 Hz, J_2=6.8 Hz, J_3=3.3 Hz, 4 H), 3.27 (br. s., 1 H), 1.57 - 1.50 (m, 2 H), 1.48 (s, 9 H), 1.45 - 1.37 (m, 2 H), 1.12 - 1.01 (m, 18 H), 0.99 - 0.92 (m, 3 H).

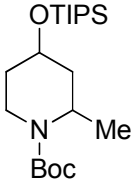
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.1, 79.2, 67.9, 35.1, 28.9, 18.6, 18.4, 13.2, 12.9, 12.6.

MS (70 eV) *m/z* (%): 259 (15), 258 (77), 215 (18), 214 (100), 131 (13), 56 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2944 (m), 2866 (m), 1698 (vs), 1464 (m), 1420 (s), 1366 (m), 1274 (m), 1230 (s), 1172 (s), 1110 (s), 1086 (s), 1068 (s), 1044 (vs), 1012 (m), 994 (m), 882 (s), 870 (s), 850 (m), 802 (m), 678 (s), 658 (s), 632 (m).

HRMS (ESI) for **$C_{19}H_{39}NO_3SiNa^+$** (380.2591) [M+Na$^+$]: 380.2592.

***t*- butyl 2-methyl-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate**



A solution of *t*-butyl 4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (17 mmol; 6.08 g) and TMEDA (17 mmol; 1.97 g; 2.53 mL) in anhydrous Et_2O (60 mL) was cooled to -78 °C.

s-BuLi (1.07 M in hexanes) (20.4 mmol; 19.07 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before $MgCl_2$ (0.5 M in THF) (8.5 mmol; 17 mL) was added. After the addition was complete, CuCN·2 LiCl (1 M in THF) (17 mmol; 17 mL) was dropped to the reaction mixture. The reaction mixture was stirred for 15 min at -78 °C before methyl iodide (17 mmol; 2.41 g; 1.06 mL) was added. The reaction mixture was kept for 4 h at -78 °C and was then allowed to warm to room temperature. NH_4Cl sat. aq. solution (100 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 30 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography (SiO_2; *i*-hexane/Et_2O 10:1) yielding 4.87 g (77%) of the title compound as a colorless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ: 4.48 (br. s., 1 H), 4.02 (br. s., 1 H), 3.91 - 3.75 (m, 1 H), 3.39 - 3.23 (m, 1 H), 1.53 - 1.35 (m, 13 H), 1.23 - 0.69 (m, 24 H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 155.2, 79.1, 66.1, 46.6, 37.4, 34.2, 33.9, 29.0, 19.7, 18.7, 18.4, 13.2, 12.8.

MS (70 eV) *m/z* (%): 371 (1) [M^+], 273 (16), 272 (79), 230 (13), 229 (19), 228 (100), 184 (12), 142 (16), 131 (42).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942 (m), 2892 (w), 2866 (m), 1694 (s), 1464 (m), 1412 (m), 1390 (m), 1378 (m), 1364 (m), 1342 (m), 1290 (w), 1272 (w), 1250 (w), 1212 (w), 1174 (s), 1134 (m), 1112 (m), 1090 (s), 1072 (s), 1054 (vs), 1028 (m), 1004 (m), 934 (w), 918 (w), 882 (s), 864 (m), 800 (w), 768 (w), 674 (s), 656 (s).

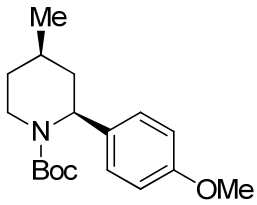
HRMS (ESI) for **$C_{20}H_{42}NO_3Si^+$** (372.2934) [M+H^+]: 372.2927.

5.2. Typical Procedure 13: Cross-Coupling of (1-(*t*-Butoxycarbonyl)-4-methylpiperidin-2-yl)zinc Chloride (TP 13) (Table 11)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of *t*-butyl 4-methylpiperidine-1-carboxylate (1 mmol; 0.20 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (2 mL). It was cooled to -78 °C and *s*-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before $ZnCl_2$ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The reaction mixture was stirred for 15 min at -78 °C and was then warmed to room temperature. Et_2O was removed *in vacuo* (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), $Pd(dba)_2$ (11.5 mg; 0.02 mmol) and S-Phos (8.2 mg; 0.02 mmol) was

prepared and stirred for 10 min. The piperidinylzinc reagent was added to this mixture at room temperature. The reaction mixture was then heated to 55 °C for 15 h. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***cis-t*-butyl 2-(4-methoxyphenyl)-4-methylpiperidine-1-carboxylate (173a)**



Cross-coupling was performed according to **TP13**.

column chromatography: SiO_2; *n*-pentane/Et_2O 4:1

yield: 167 mg (78 %)

d.r.: 99:1.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.10 (d, J=8.4 Hz, 2 H), 6.81 (d, J=8.6 Hz, 2 H), 4.91 (dd, J_1=9.4 Hz, J_2=6.4 Hz, 1 H), 4.11 (ddd, J_1=13.6 Hz, J_2=7.0 Hz, J_3=2.9 Hz, 1 H), 3.33 (s, 3 H), 3.14 (ddd, J_1=13.7 Hz, J_2=10.7 Hz, J_3=5.6 Hz, 1 H), 1.83 - 1.73 (m, 1 H), 1.66 (ddd, J_1=13.3 Hz, J_2=6.2 Hz, J_3=3.6 Hz, 1 H), 1.54 - 1.44 (m, 1 H), 1.38 (s, 9 H), 1.36 - 1.27 (m, 1 H), 0.93 - 0.84 (m, 1 H), 0.67 (d, J=6.8 Hz, 3 H).

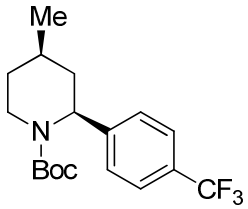
^{13}C-NMR (101 MHz, C_6D_6) δ: 159.1, 156.1, 137.5, 127.2, 114.3, 79.2, 56.7, 55.1, 38.8, 38.6, 31.7, 28.8, 27.0, 21.8.

MS (70 eV, EI) *m/z* (%): 305 (2) [M^+], 250 (10), 249 (67), 248 (23), 205 (14), 204 (100), 162 (10), 134 (10), 121 (15), 96 (14), 57 (28).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2951 (w), 2929 (w), 1686 (vs), 1612(w), 1512 (s), 1477 (w), 1455 (m), 1403 (s), 1364 (s), 1328 (m), 1292 (m), 1279 (m), 1243 (vs), 1173 (s), 1148 (vs), 1126 (m), 1112 (m), 1090 (m), 1066 (m), 1035(s), 1000 (w),864 (m), 827 (s), 775 (m), 758 (m).

HRMS (EI) for **$C_{18}H_{27}NO_3$** (305.1991): 305.1977.

***cis-t*-butyl 4-methyl-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (173b)**



Cross-coupling was performed according to **TP13**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1

yield: 195 mg (81 %)

d.r.: 95:5.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.39 (d, J=8.0 Hz, 2 H), 7.00 (d, J=8.2 Hz, 2 H), 4.68 (dd, J_1=9.8 Hz, J_2=6.3 Hz, 1 H), 3.90 (ddd, J_1=13.7, J_2=6.6 Hz, J_3=3.9 Hz, 1 H), 3.08 (ddd, J_1=13.9 Hz, J_2=10.0 Hz, J_3=5.5 Hz, 1 H), 1.69 (dddd, J_1=13.3 Hz, J_2=10.0 Hz, J_3=6.9 Hz, J_4=6.7 Hz, 1 H), 1.55 - 1.49 (m, 1 H), 1.42 - 1.33 (m, 1 H), 1.29 (s, 9 H), 1.05 (dt, J_1=13.5 Hz, J_2=10.4 Hz, 1 H), 0.88 - 0.80 (m, 1 H), 0.62 (d, J=6.8 Hz, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 155.9, 150.0 (d, J=1.0 Hz), 129.1 (q, J=32.1 Hz), 126.4, 125.8 (q, J=3.8 Hz), 125.5 (q, J=271.7 Hz), 79.6, 57.3, 39.5, 38.7, 31.6, 28.6, 27.2, 21.8.

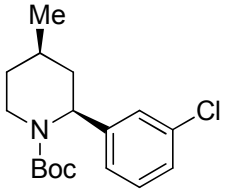
^{19}F-NMR (376 MHz, C_6D_6) δ: -61.98 (s).

MS (70 eV, EI) *m/z* (%): 343 (1) [M^+], 288 (19), 287 (73), 270 (16), 268 (11), 243 (15), 242 (64), 228 (12), 200 (23), 199 (10), 187 (12), 186 (15), 172 (21), 159 (30), 142 (28), 98 (24), 97 (14), 57 (100), 55 (10), 41 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929 (w), 2871 (w), 1688 (s), 1619 (w), 1478 (w), 1455 (w), 1415 (m), 1402 (m), 1392 (m), 1378 (w), 1365 (m), 1349 (w), 1323 (vs), 1290 (w), 1278 (w), 1243 (m), 1223 (w), 1150 (s), 1120 (vs), 1111 (vs), 1090 (m), 1066 (vs), 1016 (m), 1000 (w), 971 (w), 924 (w), 863 (w), 834 (m), 815 (w), 775 (m), 759 (w), 658 (w), 605 (w).

HRMS (EI) for **$C_{18}H_{24}F_3NO_2$** (343.1759): 343.1756.

***cis-t*-butyl 2-(3-chlorophenyl)-4-methylpiperidine-1-carboxylate (173c)**



Cross-coupling was performed according to **TP13**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1

yield: 165 mg (76 %)

d.r.: 96:4.

m.p.: 47.3 – 49.2 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.24 (s, 1 H), 7.05 (d, J=7.04 Hz, 1 H), 6.95 - 6.81 (m, 2 H), 4.64 (dd, J_1=10.1 Hz, , J_2=6.2 Hz, 1 H), 3.91 (ddd, , J_1=13.6 Hz, , J_2=6.7 Hz, , J_3=3.5 Hz, 1 H), 3.09 - 3.00 (m, 1 H), 1.73 - 1.63 (m, 1 H), 1.48 - 1.44 (m, 1 H), 1.40 - 1.33 (m, 1 H), 1.31 (s, 9 H), 1.10 - 1.00 (m, 1 H), 0.84 - 0.75 (m, 1 H), 0.61 (d, J=6.65 Hz, 3 H).

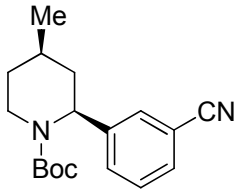
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.9, 148.2, 134.9, 130.2, 127.0, 126.5, 124.1, 79.6, 57.3, 39.4, 38.7, 31.6, 28.7, 27.1, 21.8.

MS (70 eV, EI) *m/z* (%): 309 (1) [M^+], 255 (26), 254 (15), 253 (79), 236 (15), 210 (28), 209 (16), 208 (87), 194 (12), 192 (10), 166 (19), 153 (10), 152 (11), 142 (27), 138 (14), 125 (21), 98 (37), 97 (18), 57 (100), 41 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2916 (s), 2850 (m), 1682 (vs), 1476 (m), 1398 (s), 1362 (s), 1338 (m), 1284 (s), 1244 (s), 1174 (s), 1148 (vs), 1122 (s), 1098 (s), 1088 (s), 1078 (s), 1034 (m), 1004 (m), 906 (m), 864 (s), 852 (s), 790 (s), 778 (vs), 756 (s), 710 (s), 694 (vs), 676 (m).

HRMS (EI) for **$C_{17}H_{24}ClNO_2$** (309.1496): 309.1487.

***cis-t*-butyl 2-(3-cyanophenyl)-4-methylpiperidine-1-carboxylate (173d)**



Cross-coupling was performed according to **TP13**.

column chromatography: SiO_2; *n*-pentane/Et_2O 4:1

yield: 135 mg (64 %)

d.r.: 97:3.

m.p.: 77.8 – 79.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.22 (s, 1 H), 7.08 - 6.91 (m, 2 H), 6.76 (t, J=7.7 Hz, 1 H), 4.49 (dd, J_1=10.4 Hz, J_2=5.9 Hz, 1 H), 3.79 (ddd, J_1=13.7 Hz, J_2=6.6 Hz, J_3=3.9 Hz, 1 H), 2.98 (ddd, J_1=13.7 Hz, J_2=9.8 Hz, J_3=5.6 Hz, 1 H), 1.71 - 1.59 (m, 1 H), 1.40 - 1.29 (m, 2 H), 1.29 - 1.15 (m, 9 H), 0.90 (dt, J_1=13.1 Hz, J_2=10.6 Hz, 1 H), 0.83 - 0.74 (m, 1 H), 0.60 (d, J=6.6 Hz, 3 H).

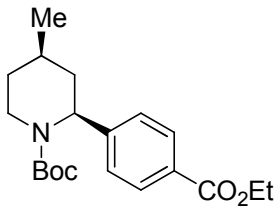
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.1, 146.4, 129.6, 129.1, 128.9, 128.6, 118.6, 112.6, 79.0, 56.5, 39.0, 37.9, 30.8, 27.8, 26.5, 21.1.

MS (70 eV, EI) *m/z* (%): 300 (1) [M^+], 245 (16), 244 (37), 227 (11), 200 (32), 199 (100), 185 (17), 171 (12), 157 (24), 144 (10), 143 (15), 142 (10), 129 (16), 116 (14), 98 (20), 57 (52), 41 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952 (w), 2920 (w), 2230 (w), 1682 (vs), 1482 (m), 1440 (w), 1404 (s), 1374 (m), 1364 (m), 1338 (w), 1328 (w), 1288 (m), 1248 (m), 1182 (m), 1150 (vs), 1122 (m), 1096 (m), 1010 (m), 924 (w), 874 (m), 862 (w), 798 (s), 778 (m), 758 (w), 734 (w), 694 (s), 636 (w).

HRMS (EI) for **$C_{18}H_{24}N_2O_2$** (300.1838): 300.1860.

***cis-t*-butyl 2-(4-(ethoxycarbonyl)phenyl)-4-methylpiperidine-1-carboxylate (173e)**



Cross-coupling was performed according to **TP13**.

column chromatography: SiO_2; *n*-pentane/Et_2O 4:1

yield: 163 mg (67 %)

d.r.: 98:2.

m.p.: 108.8 – 110.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.20 (d, *J*=8.4 Hz, 2 H), 7.12 (d, *J*=8.4 Hz, 2 H), 4.74 (dd, J_1=9.7 Hz, J_2=6.2 Hz, 1 H), 4.15 (q, *J*=7.1 Hz, 2 H), 3.96 (ddd, J_1=13.7 Hz, J_2=6.6 Hz, J_3=3.7 Hz, 1 H), 3.12 (ddd, J_1=13.7, J_2=10.2 Hz, J_3=5.4 Hz, 1 H), 1.70 (dddd, J_1=13.3 Hz, J_2=10.2 Hz, J_3=7.1 Hz, J_4=6.8 Hz, 1 H), 1.54 (ddd, J_1=13.4 Hz, J_2=5.9 Hz, J_3=3.9 Hz, 1 H), 1.43 - 1.36 (m, 1 H), 1.29 (s, 9 H), 1.13 (dt, J_1=13.4 Hz, J_2=10.2 Hz, 1 H), 1.03 (t, *J*=7.1 Hz, 3 H), 0.89 - 0.80 (m, 1 H), 0.61 (d, *J*=7.1 Hz, 3 H).

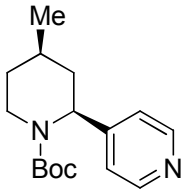
^{13}C-NMR (101 MHz, C_6D_6) δ: 166.5, 156.0, 151.1, 130.4, 129.8, 126.0, 79.6, 61.1, 57.6, 39.4, 38.7, 31.6, 28.7, 27.2, 21.8, 14.6.

MS (70 eV, EI) *m/z* (%): 347 (1) [M^+], 292 (15), 291 (81), 262 (16), 247 (11), 246 (55), 219 (15), 218 (100), 176 (10), 174 (11), 142 (14), 98 (20), 97 (17), 57 (42), 43 (10).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2928 (w), 1715 (s), 1715 (s), 1689 (vs), 1610 (w), 1476 (w), 1455 (w), 1401 (m), 1392 (m), 1364 (s), 1350 (w), 1326 (w), 1307 (m), 1271 (vs), 1245 (s), 1222 (m), 1173 (s), 1149 (s), 1121 (s), 1101 (vs), 1066 (m), 1019 (m), 852 (m), 768 (m), 757 (m), 740 (w), 705 (m).

HRMS (EI) for **$C_{20}H_{29}NO_4$** (347.2097): 347.2099.

***cis*-*t*-butyl 4-methyl-2-(pyridin-4-yl)piperidine-1-carboxylate (173f)**



Cross-coupling was performed according to **TP13**.

column chromatography: SiO_2; Et_2O

yield: 141 mg (73 %)

d.r.: 95:5.

^{1}H-NMR (300 MHz, C_6D_6) δ: 8.56 (dd, J_1=4.6 Hz, J_2=1.4 Hz, 2 H), 6.79 (d, J=5.6 Hz, 2 H), 4.62 (dd, J_1=9.3 Hz, J_2=6.4 Hz, 1 H), 3.89 (ddd, J_1=13.6 Hz, J_2=6.6 Hz, J_3=3.8 Hz, 1 H), 3.03 (ddd, J_1=13.8 Hz, J_2=10.0 Hz, J_3=5.3 Hz, 1 H), 1.72 - 1.59 (m, 1 H), 1.54 - 1.38 (m, 2 H), 1.36 - 1.18 (m, 9 H), 1.09 - 0.97 (m, 1 H), 0.81 (dddd, J_1=16.9 Hz, J_2=5.2 Hz, J_3=4.1 Hz, J_4=3.9 Hz, 1 H), 0.58 (d, J=6.9 Hz, 3 H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 155.8, 153.9, 150.7, 121.0, 79.8, 56.5, 39.3, 38.0, 31.5, 28.6, 27.1, 21.6.

MS (70 eV, EI) *m/z* (%): 276 (10) [M^+], 221 (40), 220 (78), 202 (17), 176 (55), 175 (73), 142 (35), 133 (30), 120 (17), 119 (17), 106 (16), 98 (97), 57 (100), 56 (15), 55 (19), 41 (23), 41 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (w), 2928 (w), 1688 (vs), 1598 (m), 1478 (w), 1456 (w), 1404 (s), 1364 (s), 1338 (m), 1316 (m), 1280 (m), 1246 (s), 1228 (m), 1174 (s), 1150 (vs), 1128 (m), 1092 (m), 1064 (m), 1018 (m), 994 (m), 972 (w), 862 (m), 818 (m), 800 (m), 776 (m), 760 (m), 634 (m).

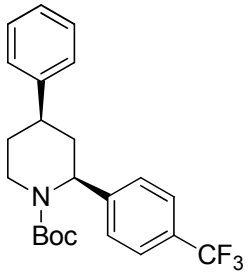
HRMS (EI) for **$C_{16}H_{24}N_2O_2$** (276.1838): 276.1830.

5.3. Typical Procedure 14: Cross-Coupling of (1-(*t*-Butoxycarbonyl)-4-phenylpiperidin-2-yl)zinc Chloride (TP 14) (Table 11)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of *t*-butyl 4-phenylpiperidine-1-carboxylate (1 mmol; 0.26 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (2 mL). It was cooled to -78 °C and *s*-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before $ZnCl_2$ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The

reaction mixture was stirred for 15 min at -78 °C and was then allowed to warm to room temperature. Et_2O was removed *in vacuo* (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), $Pd(dba)_2$ (28.8 mg; 0.05 mmol) and Ru-Phos (23.3 mg; 0.05 mmol) was prepared and stirred for 10 min. The piperidinylzinc reagent was added to this mixture at room temperature. The reaction mixture was then heated to 55 °C for 15 h. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***cis-t*-butyl 4-phenyl-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (173g)**



Cross-coupling was performed according to **TP14**.

column chromatography: SiO_2; toluene

yield: 182 mg (64 %)

d.r.: 97:3.

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.40 (d, *J*=8.3 Hz, 2 H), 7.13 (d, *J*=8.0 Hz, 2 H), 7.10 - 7.04 (m, 1 H), 6.98 (d, *J*=8.0 Hz, 2 H), 6.90 (d, *J*=7.2 Hz, 2 H), 4.65 (dd, J_1=11.6 Hz, J_2=6.1 Hz, 1 H), 3.99 (ddd, J_1=13.8 Hz, J_2=7.2 Hz, J_3=3.9 Hz, 1 H), 3.23 (ddd, J_1=13.9 Hz, J_2=9.5 Hz, J_3=6.2 Hz, 1 H), 2.58 - 2.46 (m, 1 H), 2.06 – 1.92 (m, 1 H), 1.78 - 1.69 (m, 1 H), 1.55 - 1.45 (m, 1 H), 1.43 - 1.33 (m, 1 H), 1.29 (s, 9 H).

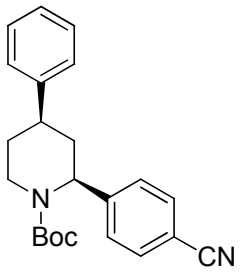
^{13}C-NMR (75 MHz, C_6D_6) δ: 155.9, 149.9 (d, *J*=1.1 Hz), 146.4, 129.3 (q, *J*=32.1 Hz), 129.2, 127.4, 127.0, 126.3, 125.9 (q, *J*=3.9 Hz), 125.5 (q, *J*=271.8 Hz), 79.8, 58.4, 40.3, 39.0, 38.6, 31.8, 28.6.

MS (70 eV, EI) *m/z* (%): 405 (1) [M^+], 350 (24), 349 (100), 304 (21), 288 (10), 200 (13), 187 (12), 186 (14), 172 (10), 159 (11), 118 (32), 104 (15), 90 (19); 59 (85); 41 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976 (w), 2932 (w), 1688 (s), 1620 (w), 1478 (w), 1454 (w), 1402 (m), 1366 (m), 1322 (vs), 1292 (m), 1248 (m), 1162 (s), 1120 (vs), 1110 (vs), 1066 (s), 1038 (w), 1016 (m), 950 (w), 878 (w), 860 (w), 836 (m), 818 (w), 760 (m), 700 (s), 662 (w).

HRMS (EI) for **$C_{23}H_{26}F_3NO_2$** (405.1916): 405.1922.

***cis-t*-butyl 2-(4-cyanophenyl)-4-phenylpiperidine-1-carboxylate (173h)**



Cross-coupling was performed according to **TP14**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1

yield: 200 mg (79 %)

d.r.: >99:1.

m.p.: 137.0-138.3 °C

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.19 – 7.15 (m, 2 H), 7.15 - 7.06 (m, 3 H), 6.89 (d, J=7.0 Hz, 2 H), 6.79 (d, J=8.2 Hz, 2 H), 4.51 (dd, J_1=11.7 Hz, J_2=6.0 Hz, 1 H), 3.91 (ddd, J_1=13.7 Hz, J_2=7.07 Hz, J_3=4.0 Hz, 1 H), 3.20 (ddd, J_1=13.8 Hz, J_1= 9.3 Hz, J_1=6.1 Hz, 1 H), 2.52 - 2.42 (m, 1 H), 2.00 - 1.90 (m, 1 H), 1.67 - 1.60 (m, 1 H), 1.45 - 1.32 (m, 2 H), 1.27 (s, 9 H).

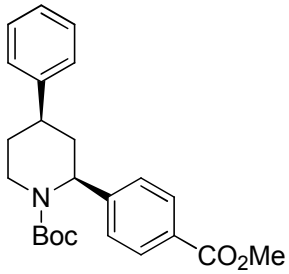
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.8, 150.7, 146.3, 132.6, 129.2, 127.4, 127.1, 126.4, 119.3, 111.3, 79.9, 58.6, 40.5, 39.0, 38.4, 31.7, 28.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2940 (w), 2922 (w), 2842 (w), 2222 (w), 1698 (s), 1604 (w), 1446 (w), 1390 (m), 1366 (m), 1328 (m), 1280 (m), 1254 (s), 1166 (s), 1150 (vs), 1094 (w), 1024 (w), 980 (w), 858 (w), 840 (m), 782 (m), 764 (m), 756 (m), 708 (m).

MS (70 eV, EI) *m/z* (%): 363 (1) [M+H$^+$], 306 (73), 262 (35), 261 (62), 184 (19), 157 (40), 144 (27), 143 (45), 129 (28), 118 (36), 116 (18), 104 (37), 91 (25), 57 (100), 41 (26).

HRMS (EI) for **$C_{23}H_{27}N_2O_2^+$** (363.2067) [M+H$^+$]: 363.2060.

***cis-t*-butyl 2-(4-(methoxycarbonyl)phenyl)-4-phenylpiperidine-1-carboxylate (173i)**



Cross-coupling was performed according to **TP14**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1

yield: 185 mg (67 %)

d.r.: 99:1.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.13 (d, J=8.4 Hz, 2 H), 7.11 - 6.98 (m, 5 H), 6.84 (d, J=7.2 Hz, 2 H), 4.63 (dd, J_1=11.7 Hz, J_2=6.0 Hz, 1 H), 4.00 (ddd, J_1=13.7 Hz, J_2= 7.4 Hz, J_3= 3.6 Hz, 1 H), 3.47 (s, 3 H), 3.21 (ddd, J_1=13.8 Hz, J_2= 9.6 Hz, J_3=6.2 Hz, 1 H), 2.52 - 2.42 (m, 1 H), 2.04 - 1.85 (m, 1 H), 1.74 - 1.67 (m, 1 H), 1.55 - 1.43 (m, 1 H), 1.36 - 1.27 (m, 1 H), 1.24 (s, 9 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 167.0, 155.9, 151.2, 146.6, 130.5, 129.6, 129.1, 127.5, 126.9, 126.0, 79.8, 58.8, 51.9, 40.2, 39.0, 38.5, 31.8, 28.7.

MS (70 eV, EI) *m/z* (%): 395 (1) [M^+], 340 (21), 339 (100), 295 (30), 294 (48), 280 (41), 190 (19), 177 (17), 176 (27), 162 (29), 118 (23), 104 (25), 91 (21); 57 (45); 41 (19).

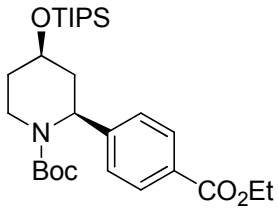
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950 (w), 1720 (s), 1690 (vs), 1610 (w), 1434 (m), 1402 (s), 1366 (m), 1324 (m), 1312 (m), 1276 (vs), 1248 (s), 1168 (s), 1148 (s), 1132 (s), 1104 (s), 1060 (w), 1018 (m), 950 (w), 878 (w), 854 (m), 772 (m), 758 (s), 700 (s).

HRMS (EI) for **$C_{24}H_{29}NO_4$** (395.2097): 395.2082.

5.4. Typical Procedure 15: Cross-Coupling of (1-(*t*-Butoxycarbonyl)-4-((triisopropylsilyl)oxy)piperidin-2-yl)zinc Chloride (TP 15) (Table 11)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of *t*-butyl 4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (1 mmol; 0.36 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (2 mL). It was cooled to -78 °C and *s*-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before $ZnCl_2$ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The reaction mixture was stirred for 15 min at -78 °C and was then allowed to warm to room temperature. Et_2O was removed *in vacuo* (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), $Pd(dba)_2$ (28.8 mg; 0.05 mmol) and Ru-Phos (23.3 mg; 0.05 mmol) was prepared and stirred for 10 min. The piperidinylzinc reagent was added to this mixture at room temperature. The reaction mixture was then heated to 55 °C for 60 h. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***cis-t*-butyl 2-(4-(ethoxycarbonyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (173j)**



Cross-coupling was performed according to **TP15**.

column chromatography: SiO_2; *n*-pentane/Et_2O 8:1

yield: 297 mg (84 %)

d.r.: 97:3.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.17 (d, *J*=8.4 Hz, 2 H), 7.20 (d, *J*=8.0 Hz, 2 H), 5.32 (dd, J_1=6.2 Hz, J_2=3.2 Hz, 1 H), 4.24 - 4.16 (m, 1 H), 4.13 (q, *J*=7.11 Hz, 2 H), 3.89 - 3.82 (m, 1 H), 3.45 (td, J_1=12.7 Hz, J_2=3.5 Hz, 1 H), 2.06 (dt, J_1=14.0 Hz, J_2=3.5 Hz, 1 H), 1.78 (ddd, J_1=14.1 Hz, J_2=7.1 Hz, J_3=3.0 Hz, 1 H), 1.58 - 1.49 (m, 1 H), 1.39 (s, 9 H), 1.31 (d, *J*=7.0 Hz, 1 H), 1.02 (t, *J*=7.0 Hz, 3 H), 0.98 - 0.77 (m, 18 H), 0.77 - 0.69 (m, 3 H).

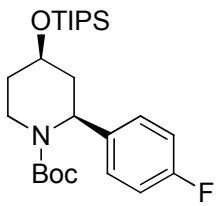
^{13}C-NMR (101 MHz, C_6D_6) δ: 166.6, 155.7, 149.7, 130.3, 129.4, 126.3, 79.8, 65.7, 61.0, 53.3, 37.7, 36.6, 33.5, 32.7, 30.5, 30.5, 30.2, 28.7, 23.5, 18.5, 18.4, 14.7, 14.7, 12.7.

MS (70 eV, EI) *m/z* (%): 505 (1) [M^+], 407 (32), 406 (100), 363 (31), 362 (91), 231 (74), 230 (85), 188 (21), 186 (85), 159 (38), 144 (23), 131 (44), 103 (21), 75 (22), 57 (29), 41 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2940 (m), 2924 (m), 2865 (m), 1717 (s), 1693 (vs), 1462 (m), 1414 (m), 1403 (m), 1390 (m), 1381 (m), 1364 (s), 1271 (vs), 1254 (m), 1214 (m), 1170 (s), 1103 (vs), 1080 (s), 1067 (s), 1044 (s), 1021 (s), 995 (m), 985 (m), 953 (m), 880 (s), 850 (m), 777 (m), 773 (m), 721 (m), 713 (m), 679 (s), 660 (s), 631 (m).

HRMS (EI) for **$C_{28}H_{47}NO_5Si$** (505.3224): 505.3221.

***cis-t*- butyl 2-(4-fluorophenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (173k)**



Cross-coupling was performed according to **TP15**.

column chromatography: SiO_2; CH_2Cl_2

yield: 275 mg (87 %)

d.r.: 95:5.

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.04 (dd, J_1=8.3 Hz, J_2=5.3 Hz, 2 H), 6.83 (t, J=8.7 Hz, 2 H), 5.30 - 5.25 (m, 1 H), 4.16 (ddd, J_1=13.3 Hz, J_2=4.7 Hz, J_3=2.9 Hz, 1 H), 3.89 - 3.83 (m, 1 H), 3.40 (td, J_1=12.7 Hz, J_2=3.5 Hz, 1 H), 2.06 - 1.97 (m, 1 H), 1.78 (ddd, J_1=14.1 Hz, J_2=6.9 Hz, J_3=3.3 Hz, 1 H), 1.63 - 1.51 (m, 1 H), 1.40 (s, 9 H), 1.11 - 1.04 (m, 1 H), 1.02 - 0.83 (m, 18 H), 0.83 - 0.73 (m, 3 H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 155.7, 162.2 (d, J=243.2 Hz), 139.9 (d, J=3.1 Hz), 127.9 (d, J=7.8 Hz), 115.4 (d, J=21.3 Hz), 79.7, 65.8, 52.8, 37.7, 36.4, 33.7, 28.8, 18.5, 18.5, 12.7.

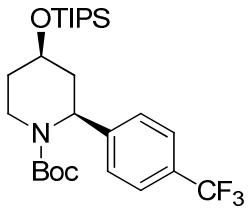
^{19}F-NMR (282 MHz, C_6D_6) δ: -116.44 - -116.36 (m) (minor), -117.97 - -117.82 (m) (major).

MS (70 eV, EI) *m/z* (%): 451 (1) [M^+], 309 (22), 308 (86), 187 (18), 186 (100), 177 (87), 176 (18), 174 (18), 173 (19), 159 (40), 157 (20), 156 (22), 150 (26), 144 (35), 142 (16), 131 (35), 103 (24), 75 (25), 41 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972 (w), 2932 (w), 2232 (w), 1684 (s), 1608 (w), 1508 (w), 1474 (w), 1454 (m), 1434 (w), 1410 (m), 1392 (m), 1380 (m), 1364 (s), 1338 (s), 1312 (m), 1280 (m), 1270 (m), 1248 (m), 1220 (m), 1156 (vs), 1104 (s), 1070 (m), 1056 (m), 1018 (m), 982 (s), 964 (m), 910 (m), 870 (m), 854 (m), 838 (s), 794 (m), 780 (m), 758 (m), 724 (w), 680 (m), 670 (m), 660 (m).

HRMS (EI) for **$C_{25}H_{42}FNO_3Si$** (451.2918): 451.2938.

***cis-t*-butyl 2-(4-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (173l)**



Cross-coupling was performed according to **TP15**.

column chromatography: SiO_2; CH_2Cl_2

yield: 284 mg (81 %)

d.r.: 95:5.

m. p.: 94.8 – 95.9°C

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.37 (d, J=8.2 Hz, 2 H), 7.10 (d, J=8.2 Hz, 2 H), 5.35 (d, J=5.1 Hz, 1 H), 4.16 (d, J=12.9 Hz, 1 H), 3.85 - 3.80 (m, 1 H), 3.39 (td, J_1=12.7 Hz, J_2=3.6 Hz, 1 H), 2.01 (d, J=14.3 Hz, 1 H), 1.73 (ddd, J_1=14.1 Hz, J_2=7.1 Hz, J_3=3.0 Hz, 1 H), 1.53 - 1.47 (m, 1 H), 1.41 (s, 9 H), 1.04 - 1.00 (m, 1 H), 0.84 - 0.80 (m, 18 H), 0.75 - 0.62 (m, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 155.7, 148.4 (d, *J*=1.0 Hz), 128.8 (q, *J*=32.3 Hz), 126.6, 125.7 (q, *J*=3.7 Hz), 125.5 (q, *J*=271.6 Hz), 79.9, 65.5, 52.7, 37.4, 36.3, 33.4, 28.7, 18.5, 18.4, 12.7.

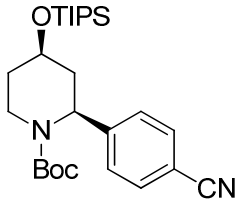
^{19}F-NMR (376 MHz, C_6D_6) δ: -62.12 (s) (major), -62.20 (s) (minor).

MS (70 eV, EI) *m/z* (%): 501 (1) [M^+], 403 (23), 402 (100), 358 (24), 230 (31), 186 (22), 131 (22), 57 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2944 (m), 2868 (m), 1696 (s), 1418 (m), 1366 (m), 1328 (vs), 1164 (s), 1126 (s), 1082 (m), 1070 (m).

HRMS (EI) for **$C_{26}H_{42}F_3NO_3Si$** (501.2886): 501.2877.

***cis-t*-butyl 2-(4-cyanophenyl)-4-((triisopropylsilyl)oxy)piperidine-1-carboxylate (173m)**



Cross-coupling was performed according to **TP15**.

column chromatography: SiO_2; *n*-pentane/Et_2O 4:1

yield: 260 mg (81 %)

d.r.: 97:3.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.09 (d, *J*=8.2 Hz, 2 H), 6.90 (d, *J*=8.0 Hz, 2 H), 5.21 (d, *J*=4.3 Hz, 1 H), 4.08 (dd, J_1=9.68 Hz, J_2=3.42 Hz, 1 H), 3.79 - 3.75 (m, 1 H), 3.28 (td, J_1=12.6 Hz, J_2=3.7 Hz, 1 H), 1.89 (d, *J*=14.1 Hz, 1 H), 1.66 (ddd, J_1=14.1 Hz, J_2=7.1 Hz, J_3=3.0 Hz, 1 H), 1.50 - 1.41 (m, 2 H), 1.39 (s, 9 H), 0.80 (t, *J*=6.9 Hz, 18 H), 0.72 - 0.63 (m, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 155.5, 149.4, 132.3, 126.9, 119.3, 110.8, 80.0, 65.4, 52.8, 37.3, 36.3, 33.3, 28.8, 28.7, 18.6, 18.4, 18.4, 12.9, 12.6, 12.3.

MS (70 eV, EI) *m/z* (%): 459 (1) [M+H^+], 360 (19), 359 (65), 316 (27), 315 (100), 230 (18), 187 (10), 186 (58), 184 (24), 159 (19), 157 (14), 156 (14), 144 (21), 131 (11), 75 (13), 57 (10).

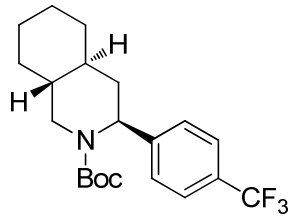
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2941 (m), 2865 (m), 1691 (vs), 1461 (m), 1414 (m), 1403 (m), 1390 (m), 1381 (m), 1364 (s), 1355 (m), 1334 (m), 1281 (m), 1252 (m), 1215 (m), 1166 (s), 1127 (m), 1117 (m), 1079 (s), 1067 (s), 1043 (s), 1021 (m), 1013 (s), 985 (s), 880 (s), 873 (s), 830 (m), 796 (m), 771 (m), 746 (m), 697 (m), 680 (s), 659 (s), 641 (m), 636 (m).

HRMS (EI) for **$C_{26}H_{43}N_2O_3Si^+$** (459.3037) [M+H^+]: 459.3022.

5.5. Typical Procedure 16: Cross-Coupling of (*trans*-2-(*t*-Butoxycarbonyl)decahydroisoquinolin-3-yl)zinc Chloride (TP 16) (Table 11)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of *trans*-*t*-butyl octahydroisoquinoline-2(1*H*)-carboxylate (1 mmol; 0.24 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (2 mL). It was cooled to -78 °C and *s*-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before $ZnCl_2$ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The reaction mixture was stirred for 15 min at -78 °C and was then allowed to warm to room temperature. Et_2O was removed *in vacuo* (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), $Pd(dba)_2$ (28.8 mg; 0.05 mmol) and Ru-Phos (23.3 mg; 0.05 mmol) was prepared and cooled to 0 °C. The piperidinylzinc reagent was added to this mixture and stirred for 4 h. The reaction mixture was then warmed to room temperature and stirred for 12 h and finally heated to 55 °C for 12 h. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

_t_-butyl 3-(4-(trifluoromethyl)phenyl)octahydroisoquinoline-2(1*H*)-carboxylate (173n)



Cross-coupling was performed according to **TP16**.

column chromatography: SiO_2; *n*-pentane/CH_2Cl_2 1:1 to 1:4

yield: 185 mg (69 %)

d.r.: >99:1.

m.p.: 104.1 – 105.5 °C.

^{1}H-NMR (599 MHz, C_6D_6) δ: 7.42 (d, J=8.2 Hz, 2 H), 7.07 (d, J=8.2 Hz, 2 H), 4.16 (dd, J_1=10.8 Hz, J_2=5.1 Hz, 1 H), 4.04 (dd, J_1=12.8 Hz, J_2=5.1 Hz, 1 H), 2.65 (dd, J_1=12.6 Hz, J_2=10.7 Hz, 1 H), 1.56 (d, J=8.0 Hz, 2 H), 1.51 (ddd, J_1=13.3 Hz, J_2=4.8 Hz, J_3=3.3 Hz, 1 H), 1.44 - 1.36 (m, 2 H), 1.17 (s, 9 H), 1.10 - 0.95 (m, 4 H), 0.79 - 0.64 (m, 3 H).

^{13}C-NMR (151 MHz, C_6D_6) δ: 156.9, 151.6 (d, *J*=1.4 Hz), 128.8 (q, *J*=32.3 Hz), 126.5, 125.7 (q, *J*=3.6 Hz), 125.6 (q, *J*=271.8 Hz), 79.8, 59.6, 52.2, 41.6, 41.0, 39.9, 33.2, 31.2, 28.4, 26.7, 26.4.

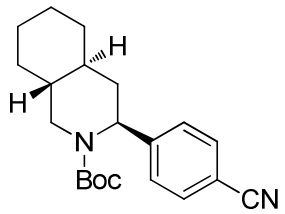
^{19}F-NMR (376 MHz, C_6D_6) δ: -61.83 (s).

MS (70 eV, EI) *m/z* (%): 383 (1) [M^+], 328 (24), 327 (100), 326 (10), 283 (27), 282 (67), 240 (13), 182 (11), 182 (18), 181 (17), 177 (35), 138 (40), 137 (19), 57 (60).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2920 (w), 2854 (w), 1680 (s), 1368 (m), 1326 (vs), 1306 (m), 1282 (m), 1258 (m), 1250 (m), 1160 (vs), 1142 (m), 1118 (vs), 1104 (s), 1090 (m), 1068 (vs), 1020 (m), 854 (m), 838 (s), 788 (m), 662 (m), 612 (m).

HRMS (EI) for **$C_{21}H_{28}F_3NO_2$** (383.2072): 383.2075.

t-butyl 3-(4-cyanophenyl)octahydroisoquinoline-2(1*H*)-carboxylate (173o)



Cross-coupling was performed according to **TP16**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1

yield: 129 mg (54 %)

d.r.: >99:1.

m.p.: 83.3 – 84.6 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.11 (m, *J*=8.4 Hz, 2 H), 6.86 (m, *J*=8.2 Hz, 2 H), 4.04 - 3.94 (m, 2 H), 2.56 (dd, J_1=12.8 Hz, J_2=10.8 Hz, 1 H), 1.55 (d, *J*=9.0 Hz, 2 H), 1.42 - 1.33 (m, 3 H), 1.14 (s, 9 H), 1.09 - 1.01 (m, 2 H), 0.96 - 0.83 (m, 2 H), 0.77 - 0.62 (m, 3 H).

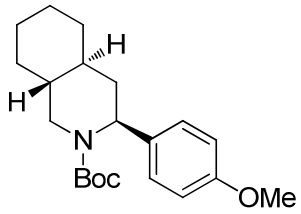
^{13}C-NMR (101 MHz, $CDCl_3$) δ: 156.6, 152.1, 132.2, 126.4, 119.2, 110.4, 79.7, 59.6, 52.1, 41.3, 40.7, 39.7, 32.9, 30.8, 28.2, 26.4, 26.1.

MS (70 eV, EI) *m/z* (%): 340 (1) [M^+], 284 (65), 240 (37), 239 (100), 182 (37), 143 (35), 138 (37), 74 (45), 59 (73), 57 (89), 45 (51), 41 (63).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922 (m), 2844 (w), 2230 (w), 1686 (vs), 1372 (m), 1364 (m), 1328 (m), 1306 (m), 1280 (m), 1252 (m), 1222 (m), 1162 (vs), 1140 (m), 1128 (m), 1118 (m), 1102 (m), 836 (m), 788 (m).

HRMS (EI) for **$C_{21}H_{28}N_2O_2$** (340.2151): 340.2151.

***t*-butyl 3-(4-methoxyphenyl)octahydroisoquinoline-2(1*H*)-carboxylate (173p)**



Cross-coupling was performed according to **TP16**.

column chromatography: SiO_2; *n*-pentane/Et_2O 6:1

yield: 145 mg (60 %)

d.r.: 97:3.

m.p.: 73.1 – 74.7 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.19 (d, J=8.0 Hz 2 H), 6.85 (d, J=8.8 Hz, 2 H), 4.50 (dd, J_1=10.1 Hz, J_2=5.6 Hz, 1 H), 4.04 (dd, J_1=13.0 Hz, J_2=5.6 Hz, 1 H), 3.36 (s, 3 H), 2.89 (dd, J_1=12.9 Hz, J_2= 9.7 Hz, 1 H), 1.75 (ddd, J_1=13.3 Hz, J_2=5.6 Hz, J_3=3.7 Hz, 1 H), 1.55 (d, J=8.0 Hz, 2 H), 1.44 (td, J_1=6.0 Hz, J_2=2.8 Hz, 2 H), 1.36 - 1.27 (m, 10 H), 1.14 - 1.01 (m, 3 H), 0.89 - 0.69 (m, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 159.0, 157.0, 139.0, 131.0, 127.4, 114.2, 79.2, 58.8, 55.2, 51.6, 41.1, 40.8, 39.9, 33.5, 31.6, 30.6, 28.7, 26.9, 26.6.

MS (70 eV, EI) *m/z* (%): 345 (2) [M^+], 290 (20), 289 (100), 288 (36), 245 (20), 244 (85), 181 (11), 137 (10), 136 (15), 121 (18), 57 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2918 (m), 2854 (m), 1684 (vs), 1510 (s), 1466 (m), 1444 (m), 1390 (m), 1366 (s), 1324 (m), 1304 (m), 1278 (m), 1238 (vs), 1224 (s), 1166 (vs), 1142 (s), 1126 (s), 1102 (s), 1090 (m), 1078 (m), 1036 (s), 1018 (m), 976 (m), 876 (m), 858 (m), 828 (vs), 816 (m), 786 (s), 764 (m).

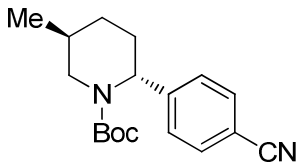
HRMS (EI) for **$C_{21}H_{31}NO_3$** (345.2304): 345.2296.

5.6. Typical Procedure 17: Cross-Coupling of (1-(*t*-Butoxycarbonyl)-5-methylpiperidin-2-yl)zinc Chloride (TP 17) (Table 11)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of *t*-butyl 3-methylpiperidine-1-carboxylate (1 mmol; 0.20 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (2 mL). It was cooled to -78 °C and *s*-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before $ZnCl_2$ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The

reaction mixture was stirred for 15 min at -78 °C and was then allowed to warm to room temperature. Et_2O was removed *in vacuo* (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), $Pd(dba)_2$ (28.8 mg; 0.05 mmol) and Ru-Phos (23.3 mg; 0.05 mmol) was prepared and cooled to 0 °C. The piperidinylzinc reagent was added to this mixture at this temperature and stirred for 6 h. It was then kept at room temperature for further 12 h and eventually heated to 40 °C for 12 h. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***trans-t*-butyl 2-(4-cyanophenyl)-5-methylpiperidine-1-carboxylate (173q)**



Cross-coupling was performed according to **TP17**.

column chromatography: SiO_2; *n*-pentane/Et_2O 4:1

yield: 128 mg (61 %)

d.r.: 96:4. (10% regioisomer)

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.04 (m, *J*=8.4 Hz, 2 H), 6.80 (d, *J*=8.0 Hz, 2 H), 5.22 (br. s., 1 H), 3.67 (d, *J*=13.6 Hz, 1 H), 2.70 (dd, J_1=13.4 Hz, J_2=3.7 Hz, 1 H), 1.78 - 1.67 (m, 1 H), 1.41 (s, 9 H), 1.39 - 1.28 (m, 3 H), 1.24 - 1.14 (m, 1 H), 0.90 (d, *J*=7.0 Hz, 3 H).

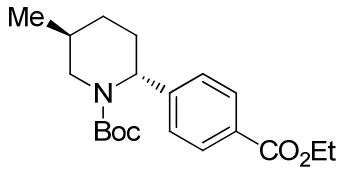
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.4, 146.3, 137.7, 132.4, 131.8, 126.7, 118.5, 110.6, 79.0, 53.5, 45.1, 28.0, 27.7, 25.7, 23.0, 17.0.

MS (70 eV, EI) *m/z* (%): 300 (1) [M^+], 245 (23), 244 (87), 227 (17), 200 (30), 199 (96), 143 (11), 142 (32), 129 (16), 116 (26), 98 (11), 57 (100), 43 (18), 41 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960 (w), 2928 (w), 2228 (w), 1684 (s), 1476 (w), 1456 (m), 1414 (s), 1392 (m), 1364 (s), 1328 (m), 1246 (m), 1172 (s), 1142 (vs), 1102 (w), 1084 (m), 1058 (m), 1018 (w), 990 (m), 878 (w), 854 (m), 838 (m), 768 (m).

HRMS (EI) for **$C_{18}H_{24}N_2O_2$** (300.1838): 300.1840.

***trans-t*-butyl 2-(4-(ethoxycarbonyl)phenyl)-5-methylpiperidine-1-carboxylate (173r)**



Cross-coupling was performed according to **TP17**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1

yield: 153 mg (63 %)

d.r.: 95:5.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.17 (d, *J*=8.4 Hz, 2 H), 7.15 (d., 2 H), 5.41 (br. s., 1 H), 4.15 (q, *J*=7.0 Hz, 2 H), 3.78 (d, *J*=13.4 Hz, 1 H), 2.88 (dd, J_1=13.5 Hz, J_2=3.6 Hz, 1 H), 1.87 - 1.77 (m, 1 H), 1.62 - 1.54 (m, 1 H), 1.49-1.43 (m, 10 H), 1.40 - 1.27 (m, 2 H), 1.03 (t, *J*=7.1 Hz, 3 H), 0.94 (d, *J*=7.0 Hz, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 166.5, 156.3, 147.2, 130.6, 130.5, 130.4, 129.8, 127.1, 79.6, 61.1, 54.4, 45.8, 28.8, 28.5, 26.5, 23.9, 17.8, 14.7.

MS (70 eV, EI) *m/z* (%): 347 (1) [M^+], 292 (16), 291 (92), 262 (17), 247 (11), 246 (53), 219 (15), 218 (100), 142 (13), 98 (12), 57 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2964 (w), 2932 (w), 1716 (s), 1686 (vs), 1610 (w), 1476 (w), 1456 (m), 1416 (s), 1392 (m), 1364 (s), 1342 (w), 1324 (m), 1312 (m), 1270 (vs), 1246 (s), 1172 (s), 1142 (vs), 1122 (s), 1102 (vs), 1058 (m), 1018 (s), 988 (m), 892 (w), 878 (m), 864 (m), 836 (w), 766 (m), 746 (m), 724 (w), 696 (m).

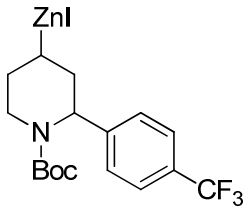
HRMS (EI) for **$C_{20}H_{29}NO_4$** (347.2097): 347.2096.

5.7. Typical Procedure 18: Preparation of Piperidin-4-ylzinc Iodides (TP 18) (Table 12)

Anhydrous LiCl (4.5 mmol; 0.19 g) was placed in an Ar-flushed flask and dried for 20 min at 150-170 °C under high vacuum (1 mbar). Zn powder (9 mmol; 0.59 g; 150 mesh, Chemetall) was added under Ar and the heterogeneous mixture of Zn and LiCl was dried again under vigorous stirring for 20 min at 150-170 °C under high vacuum (1 mbar). The reaction mixture was evacuated and refilled with Ar three times. A catalytic amount of 1,2-dibromoethane and THF (6 mL) were added. The mixture was gently heated in order to activate the Zn surface. The respective 4-iodopiperidine was added neat at room temperature. The resulting reaction mixture was stirred for 4 h at ambient temperature. It was then separated from the remaining

Zn powder via syringe filter (25 mm with 1 μm glass fiber membrane) and transferred to an Ar-flushed Schlenk flask. The concentrations of all piperidinylzinc reagents were determined via titration with I_2 (50 mg in 2 mL THF).

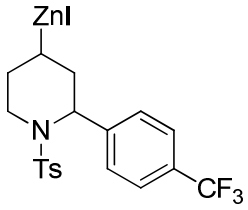
(1-(*t*-butoxycarbonyl)-2-(4-(trifluoromethyl)phenyl)-piperidin-4-yl)zinc iodide (174a)



Zn-insertion was performed according to **TP18**.

0.35 M (70%)

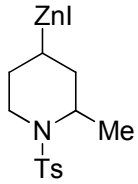
(1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)zinc iodide (174b)



Zn-insertion was performed according to **TP18**.

0.39 M (78%)

(2-methyl-1-tosylpiperidin-4-yl)zinc iodide (174c)



Zn-insertion was performed according to **TP18**.

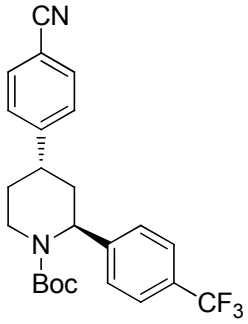
0.42 M (84%)

5.8. Typical Procedure 19: Cross-Coupling of Piperidin-4-ylzinc Iodides (TP 19) (Table 12)

A dry and Ar-flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar and a septum was charged with $TMPP_2PdCl_2$ (0.05 mmol; 63 mg), the respective aryl iodide (0.8

mmol), THF (0.8 mL) and NEP (0.02 mL). The mixture was stirred for 5 min at room temperature and then cooled to -10 °C. The corresponding piperidin-4-ylzinc iodide (0.36 – 0.39 M solution in THF) was slowly added via syringe. The reaction mixture was kept for 12 h at -10 °C and subsequently 5 h at -5 °C. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***trans-t*-butyl 4-(4-cyanophenyl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (176a)**



Cross-coupling was performed according to **TP19**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1 to 2:1

yield: 255 mg (74 %)

d.r.: 91:9.

m.p.: 72.9 – 74.6 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.42 (d, *J*=8.2 Hz, 2 H), 7.08 (d, *J*=8.2 Hz, 2 H), 7.04 (d, *J*=8.0 Hz, 2 H), 6.55 (d, *J*=8.0 Hz, 2 H), 5.59 (br. s., 1 H), 4.21 (br. s., 1 H), 2.66 - 2.57 (m, 1 H), 2.22 - 2.12 (m, 1 H), 1.93 (d, *J*=13.7 Hz, 1 H), 1.59 (td, J_1=13.4 Hz, J_2= 5.5 Hz, 1 H), 1.49 (s, 9 H), 1.33 - 1.20 (m, 2 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 154.7, 149.7, 144.2, 131.8, 129.0 (q, *J*=32.5 Hz), 126.9, 126.6, 125.5 (q, *J*=3.7 Hz), 124.4 (q, *J*=271.9 Hz), 118.1, 110.9, 79.6, 52.9, 39.9, 36.9, 34.7, 32.1, 28.0.

^{19}F-NMR (282 MHz, C_6D_6) δ: -62.14 (s) (minor), -62.19 (s) (major)

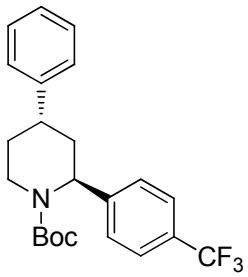
MS (70 eV) *m/z* (%): 330 (20), 329 (19), 328 (11), 311 (14), 227 (19), 213 (33), 207 (21), 200 (32), 188 (11), 187 (59), 186 (100), 185 (17), 173 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976 (vw), 2932 (w), 2868 (vw), 2228 (w), 1686 (s), 1620 (w), 1608 (w), 1506 (vw), 1478 (vw), 1454 (w), 1414 (m), 1366 (m), 1326 (vs), 1282 (m), 1258 (w),

1236 (w), 1218 (w), 1156 (vs), 1118 (vs), 1068 (s), 1016 (m), 986 (w), 968 (w), 912 (w), 886 (w), 862 (w), 834 (s), 810 (w), 770 (w), 728 (w), 722 (w).

HRMS (ESI) for $\mathbf{C_{24}H_{25}F_3N_2O_2Cl^-}$ (465.1557) [M+Cl$^-$]: 465.1564.

***trans-t*-butyl 4-phenyl-2-(4-(trifluoromethyl)phenyl)-piperidine-1-carboxylate (176b)**



Cross-coupling was performed according to **TP19**.

column chromatography: SiO_2; CH_2Cl_2

yield: 162 mg (50 %)

d.r.: 92:8.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.41 (d, J=8.2 Hz, 2 H), 7.16 - 7.02 (m, 5 H), 6.91 (d, J=7.4 Hz, 2 H), 5.63 (br. s., 1 H), 4.25 (br. s., 1 H), 2.73 - 2.65 (m, 1 H), 2.38 (t, J=11.7 Hz, 1 H), 2.15 (d, J=13.7 Hz, 1 H), 1.83 (td, J_1=13.3 Hz, J_2=5.5 Hz, 1 H), 1.54 - 1.40 (m, 11 H).

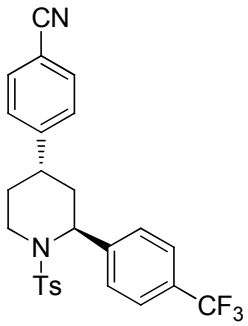
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.7, 146.1, 145.6, 129.7 (q, J=32.5 Hz), 129.2, 127.6, 127.3, 127.1, 126.2 (q, J=3.9 Hz), 126.1 (q, J=271.8 Hz), 80.1, 54.1, 41.2, 37.8, 36.2, 33.7, 28.9.

MS (70 eV, EI) *m/z* (%): 405 (1) [M$^+$], 350 (22), 349 (100), 304 (21), 200 (14), 187 (10), 186 (12), 159 (10), 118 (37), 104 (15), 90 (19), 59 (89), 41 (13); 18 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976 (w), 2932 (w), 2868 (vw), 1688 (s), 1620 (w), 1494 (vw), 1478 (w), 1454 (w), 1414 (m), 1394 (m), 1366 (m), 1324 (vs), 1300 (m), 1282 (m), 1268 (m), 1256 (w), 1234 (m), 1214 (w), 1154(s), 1118 (vs), 1068 (s), 1016 (s), 986 (w), 964 (w), 912 (w), 888 (w), 862 (w), 838 (m), 760 (m), 730 (w), 722 (w), 698 (s), 638 (w).

HRMS (EI) for $\mathbf{C_{23}H_{26}F_3NO_2}$ (405.1916): 405.1932.

4-(*trans*-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzonitrile (176c)



Cross-coupling was performed according to **TP19**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1 to 1:1

yield: 271 mg (70 %)

d.r.: >99:1.

m.p.: 181.7 – 183.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.74 (d, *J*=8.2 Hz, 2 H), 7.35 (d, *J*=8.4 Hz, 2 H), 7.07 (d, *J*=8.2 Hz, 2 H), 6.98 (m, *J*=8.4 Hz, 2 H), 6.83 (d, *J*=8.0 Hz, 2 H), 6.35 (d, *J*=8.2 Hz, 2 H), 5.38 (d, *J*=3.3 Hz, 1 H), 3.97 - 3.85 (m, 1 H), 2.69 - 2.58 (m, 1 H), 2.05 - 1.96 (m, 1 H), 1.94 (s, 3 H), 1.76 (d, *J*=13.8 Hz, 1 H), 1.51 (td, J_1=13.4 Hz, J_2=5.3 Hz, 1 H), 1.16 (qd, J_1=12.7 Hz, J_2=4.4 Hz, 1 H), 0.95 (d, *J*=12.9 Hz, 1 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 150.0, 143.7, 143.5 (d, *J*=1.1 Hz), 139.6, 132.7, 130.3, 129.9 (q, *J*=32.2 Hz), 127.8, 127.7, 127.7, 126.3 (q, *J*=3.7 Hz), 125.2 (q, *J*=271.7 Hz), 119.1, 111.5, 55.5, 42.0, 37.0, 34.4, 31.8, 21.5.

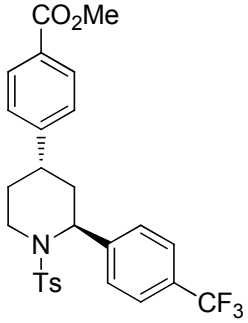
^{19}F-NMR (282 MHz, C_6D_6) δ: -62.16 (s).

MS (70 eV) *m/z* (%): 386 (37), 377 (25), 376 (100), 375 (21), 374 (16), 329 (17), 281 (10), 208 (13), 207 (56), 200 (14), 199 (12), 186 (43); 172 (13); 159 (29); 155 (21); 131 (20); 103 (10), 92 (10); 91 (73).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (w), 2930 (w), 2232 (m), 1412 (w), 1326 (vs), 1256 (m), 1158 (vs), 1110 (s), 1094 (s), 1072 (s), 1018 (s), 944 (m), 928 (s), 906 (m), 838 (s), 826 (s), 800 (m), 716 (s), 702 (s), 664 (vs), 650 (s).

HRMS (ESI) for **$C_{26}H_{23}F_3N_2O_2SCl^-$** (519.1126) [M+Cl$^-$]: 519.1122.

methyl 4-(*trans*-1-tosyl-2-(4-(trifluoromethyl)phenyl)-piperidin-4-yl)benzoate (176d)



Cross-coupling was performed according to **TP19**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1 to 1:1

yield: 286 mg (69 %)

d.r.: 97:3.

m.p.: 68.8 – 70.5 °C.

^{1}H-NMR (300 MHz, C_6D_6) δ: 8.06 (d, *J*=8.2 Hz, 2 H), 7.76 (d, *J*=8.2 Hz, 2 H), 7.36 (d, *J*=8.2 Hz, 2 H), 7.14 (d, *J*=8.0 Hz, 3 H), 6.83 (d, *J*=8.0 Hz, 2 H), 6.68 (d, *J*=8.2 Hz, 2 H), 5.40 (d, *J*=3.4 Hz, 1 H), 3.94 (d, *J*=14.2 Hz, 1 H), 3.51 (s, 3 H), 2.74 - 2.63 (m, 1 H), 2.25 - 2.13 (m, 1 H), 1.94 (s, 3 H), 1.87 (br. s., 1 H), 1.63 (dd, J_1=13.4 Hz, J_2=5.3 Hz, 2 H), 1.34 - 1.25 (m, 1 H), 1.08 (d, *J*=14.6 Hz, 1 H).

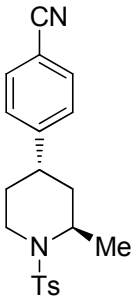
^{13}C-NMR (75 MHz, C_6D_6) δ: 166.8, 150.5, 143.7 (d, *J*=1.2 Hz), 143.6, 139.8, 130.6, 130.2, 129.8 (q, *J*=32.3 Hz), 129.7, 128.0, 127.8, 127.2, 126.3 (q, *J*=3.8 Hz), 125.3 (q, *J*=272.0 Hz), 55.7, 52.0, 42.2, 37.1, 34.4, 31.9, 21.5.

MS (70 eV, EI) *m/z* (%): 517 (11) [M^+], 371 (35), 362 (24), 361 (100), 360 (27), 359 (12), 186 (21), 155 (11), 90 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952 (vw), 2930 (vw), 2876 (vw), 1718 (s), 1610 (w), 1494 (vw), 1450 (w), 1436 (w), 1412 (w), 1326 (vs), 1278 (s), 1182 (w), 1156 (vs), 1114 (vs), 1096 (s), 1068 (s), 1016 (m), 954 (w), 932 (s), 908 (m), 840 (m), 816 (m), 802 (w), 770 (m), 742 (m), 716 (m), 708 (m), 690 (s), 658 (s), 646 (m).

HRMS (EI) for **$C_{27}H_{26}F_3NO_4S$** (517.1535): 517.1537.

4-(*trans*-2-methyl-1-tosylpiperidin-4-yl)benzonitrile (176e)



Cross-coupling was performed according to **TP19**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1 to 1:1

yield: 238 mg (84 %)

d.r.: 97:3.

m.p.: 106.2 – 107.1 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.77 (d, J=8.2 Hz, 2 H), 7.01 (m, J=8.2 Hz, 2 H), 6.85 (m, J=8.0 Hz, 2 H), 6.43 (d, J=8.2 Hz, 2 H), 4.41 - 4.33 (m, J_1=6.2 Hz, J_2=6.2 Hz, J_3=6.1 Hz, J_4=5.9 Hz, 1 H), 3.86 - 3.78 (m, 1 H), 2.64 (td, J_1=12.9 Hz, J_1= 3.0 Hz, 1 H), 2.24 - 2.15 (m, J_1=12.5 Hz, J_2=12.5 Hz, J_3=3.7 Hz, J_4=3.5 Hz, 1 H), 1.94 (s, 3 H), 1.38 (td, J_1=13.1 Hz, J_2=5.3 Hz, 1 H), 1.25 - 1.12 (m, 1 H), 1.12 - 1.06 (m, 1 H), 1.03 (dt, J_1=13.1 Hz, J_2=1.6 Hz, 1 H), 0.80 (d, J=6.8 Hz, 3 H).

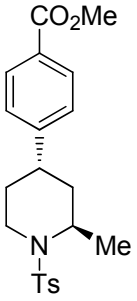
^{13}C-NMR (101 MHz, C_6D_6) δ: 150.6, 143.1, 139.9, 132.6, 130.1, 128.0, 127.8, 119.3, 111.3, 48.8, 40.3, 37.8, 36.5, 32.6, 21.5, 15.6.

MS (70 eV, EI) *m/z* (%): 354 (3) [M^+], 340 (21), 339 (100), 155 (35), 90 (47), 58 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982 (vw), 2946 (vw), 2918 (vw), 2868 (vw), 2226 (w), 1604 (w), 1504 (w), 1446 (vw), 1370 (w), 1348 (w), 1332 (m), 1316 (w), 1302 (w), 1290 (w), 1276 (w), 1256 (w), 1206 (w), 1178 (w), 1158 (s), 1148 (m), 1118 (w), 1104 (w), 1092 (m), 1070 (m), 1056 (w), 1018 (w), 1012 (w), 996 (m), 972 (m), 930 (m), 880 (w), 858 (m),848 (w), 828 (m), 816 (m), 800 (w), 722 (w), 710 (s), 698 (s), 652 (s), 624 (w).

HRMS (EI) for **$C_{20}H_{22}N_2O_2S$** (354.1402): 354.1384.

methyl 4-(*trans*-2-methyl-1-tosylpiperidin-4-yl)benzoate (176f)



Cross-coupling was performed according to **TP19**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1 to 1:1

yield: 276 mg (89 %)

d.r.: 97:3.

m.p.: 129.8 – 131.5 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.08 (d, J=8.4 Hz, 2 H), 7.78 (m, J=8.2 Hz, 2 H), 6.84 (m, J=8.0 Hz, 2 H), 6.75 (d, J=8.4 Hz, 2 H), 4.39 (qd, J_1=6.2 Hz, J_2=6.0 Hz, 1 H), 3.88 - 3.81 (m, 1 H), 3.52 (s, 3 H), 2.69 (td, J_1=12.9 Hz, J_2=3.0 Hz, 1 H), 2.36 (tt, J_1=12.5 Hz, J_2=3.6 Hz, 1 H), 1.93 (s, 3 H), 1.51 (td, J_1=13.1 Hz, J_2=5.3 Hz, 1 H), 1.36 - 1.25 (m, 1 H), 1.25 - 1.19 (m, 1 H), 1.15 (dt, J_1=13.1 Hz, J_2=1.7 Hz, 1 H), 0.84 (d, J=7.0 Hz, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 167.0, 151.1, 143.0, 140.0, 130.5, 130.1, 129.5, 127.8, 127.5, 51.9, 49.0, 40.5, 38.0, 36.5, 32.8, 21.5, 15.7.

MS (70 eV, EI) *m/z* (%): 387 (3) [M^+], 372 (23), 371 (100), 210 (8), 155 (23), 90 (33), 58 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984 (vw), 2960 (w), 2936 (w), 2910 (w), 2856 (w), 1720 (s), 1608 (w), 1596 (w), 1434 (m), 1380 (w), 1330 (m), 1304 (m), 1280 (vs), 1252 (m), 1210 (w), 1198 (w), 1188 (w), 1174 (m), 1156 (vs), 1142 (s), 1110 (m), 1094 (s), 1070 (m), 1056 (m), 1018 (w), 994 (m), 970 (m), 958 (w), 926 (m), 882 (w), 864 (m), 848 (m), 824 (w), 814 (m), 798 (w), 770 (m), 704 (s), 684 (s), 648 (m).

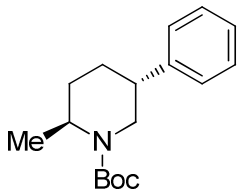
HRMS (EI) for **$C_{21}H_{25}NO_4S$** (387.1504): 387.1512.

5.9. Typical Procedure 20: Cross-Coupling of (1-(*t*-Butoxycarbonyl)-6-methylpiperidin-2-yl)zinc Chloride (TP 20) (Scheme 45)

A dry and Ar-flushed 10 mL Schlenk-tube equipped with a stirring bar was charged with a solution of *t*- butyl 2-methylpiperidine-1-carboxylate (1 mmol; 0.20 g) and TMEDA (1 mmol; 0.12 g; 0.45 mL) in anhydrous Et_2O (2 mL). It was cooled to -78 °C and *s*-BuLi (1.14 M in hexanes) (1.2 mmol; 1.05 mL) was slowly added via syringe. The reaction mixture was stirred for 4 h at this temperature before $ZnCl_2$ (1.0 M in THF) (1.2 mmol; 1.2 mL) was added. The reaction mixture was stirred for 15 min at -78 °C and was then allowed to warm to room temperature. Et_2O was removed *in vacuo* (8 min; 1 mbar). Meanwhile, a solution of the respective aryl iodide (0.7 mmol), $Pd(dba)_2$ (28.8 mg; 0.05 mmol) and Ru-Phos (23.3 mg; 0.05 mmol) was prepared and cooled to 0 °C. The piperidinylzinc reagent was added to this mixture and stirred for 12 h. The reaction mixture was then warmed to room temperature and

stirred for 12 h and finally heated to 40 °C for 12 h. NH_4Cl sat. aq. solution (20 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***trans-t*-butyl 2-methyl-5-phenylpiperidine-1-carboxylate (181a)**



Cross-coupling was performed according to **TP20**.

column chromatography: SiO_2; CH_2Cl_2

yield: 173 mg (90 %)

d.r.: 93:7.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.34 (d, *J*=7.6 Hz, 2 H), 7.21 (t, *J*=7.7 Hz, 2 H), 7.08 (t, *J*=7.4 Hz, 1 H), 4.41 - 4.33 (m, 2 H), 3.10 (dd, J_1=14.0 Hz, J_2=4.3 Hz, 1 H), 2.59 (br. s., 1 H), 1.75 - 1.58 (m, 3 H), 1.58 - 1.39 (m, 9 H), 1.05 (d, *J*=6.8 Hz, 3 H), 0.94 - 0.88 (m, 1 H).

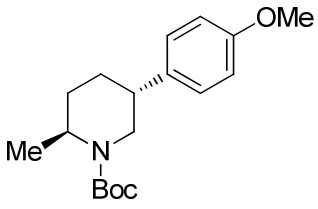
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.2, 144.7, 128.9, 128.7, 128.3, 126.6, 126.4, 79.2, 47.3, 42.5, 38.6, 28.9, 26.3, 26.1, 16.9.

MS (70 eV, EI) *m/z* (%): 275 (1) [M^+], 219 (29), 204 (44), 160 (24), 104 (16), 102 (17), 97 (24), 85 (24), 83 (22), 71 (31), 69 (24), 59 (26), 57 (100), 55 (28), 43 (24), 41 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930 (m), 2920 (w), 1684 (vs), 1452 (m), 1414 (m), 1390 (m), 1364 (s), 1338 (m), 1326 (m), 1308 (m), 1278 (m), 1240 (s), 1166 (s), 1148 (s), 1116 (s), 1078 (m), 1068 (m), 1050 (m), 1036 (m), 874 (m), 860 (m), 838 (m), 828 (m), 786 (m), 766 (m), 734 (m), 698 (s), 640 (w).

HRMS (EI) for **$C_{19}H_{25}NO_2$** (275.1885): 275.1874.

***trans-t*-butyl 5-(4-methoxyphenyl)-2-methylpiperidine-1-carboxylate (181b)**



Cross-coupling was performed according to **TP20**.

column chromatography: SiO_2; *n*-pentane/Et_2O 8:1

yield: 130 mg (61 %)

d.r.: 94:6.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.27 (d, J=8.5 Hz, 2 H), 6.84 (d, J=8.5 Hz, 2 H), 4.42 - 4.33 (m, 2 H), 3.34 (s, 3 H), 3.14 (dd, J_1=13.9 Hz, J_2=4.3 Hz, 1 H), 2.64 - 2.59 (m, 1 H), 1.77 - 1.60 (m, 3 H), 1.58 - 1.52 (m, 1 H), 1.48 (s, 9 H), 1.07 (d, J=6.8 Hz, 3 H).

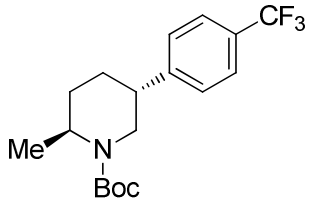
^{13}C-NMR (101 MHz, C_6D_6) δ: 158.8, 155.3, 136.4, 129.2, 127.4, 114.4, 114.3, 79.2, 55.1, 47.3, 42.7, 37.8, 29.0, 28.8, 26.3, 16.9.

MS (70 eV, EI) *m/z* (%): 305 (13) [M^+], 249 (79), 234 (36), 232 (23), 204 (32), 190 (29), 175 (21), 148 (35), 147 (22), 134 (57), 121 (46), 102 (37), 91 (23), 58 (31), 57 (100), 43 (79), 41 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972 (w), 2934 (w), 1684 (vs), 1612 (m), 1512 (s), 1456 (m), 1412 (s), 1390 (m), 1364 (s), 1340 (m), 1306 (m), 1246 (vs), 1168 (vs), 1148 (vs), 1114 (s), 1090 (m), 1036 (s), 878 (m), 828 (s), 808 (m), 768 (m).

HRMS (EI) for **$C_{18}H_{27}NO_3$** (305.1991): 305.1990.

***trans-t*-butyl 2-methyl-5-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (181c)**



Cross-coupling was performed according to **TP20**.

column chromatography: SiO_2; CH_2Cl_2

yield: 197 mg (82 %)

d.r.: 96:4.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.39 (d, J=8.2 Hz, 2 H), 7.18 (d, 2 H), 4.36 - 4.30 (m, 1 H), 4.26 (d, J=14.4 Hz, 1 H), 2.98 (dd, J_1=14.1 Hz, J_2=4.4 Hz, 1 H), 2.41 (br. s., 1 H), 1.65 - 1.54 (m, 1 H), 1.49 - 1.39 (m, 9 H), 1.35 (td, J_1=11.6 Hz, J_2=4.8 Hz, 2 H), 1.01 (d, J=6.8 Hz, 3 H), 0.85 (ddd, J_1=12.7 Hz, J_2=4.3 Hz, J_3=4.1 Hz, 1 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 155.1, 148.7 (d, J=1.1 Hz), 128.8 (q, J=32.2 Hz), 128.0, 125.7 (q, J=3.8 Hz), 125.5 (q, J=271.7 Hz), 79.5, 47.1, 41.7, 38.2, 28.9, 26.1, 25.8, 16.6.

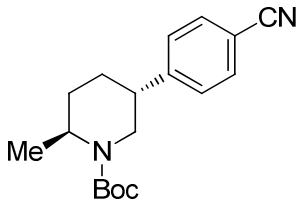
^{19}F-NMR (376 MHz, C_6D_6) δ: -61.92 (s) (minor), -62.05 (s) (major).

MS (70 eV, EI) *m/z* (%): 343 (2) [M^+], 288 (12), 287 (31), 273 (13), 272 (100), 270 (16), 242 (10), 228 (52), 172 (14), 57 (82).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980 (w), 2930 (w), 1680 (s), 1412 (m), 1366 (m), 1328 (s), 1310 (m), 1254 (m), 1236 (m), 1162 (s), 1148 (s), 1116 (vs), 1090 (s), 1070 (s), 1054 (m), 1038 (m), 1018 (m), 882 (m), 866 (m), 834 (s), 768 (m), 708 (m), 648 (m).

HRMS (EI) for **$C_{18}H_{24}F_3NO_2$** (343.1759): 343.1757.

***trans-t*-butyl 5-(4-cyanophenyl)-2-methylpiperidine-1-carboxylate (181d)**



Cross-coupling was performed according to **TP20**.

column chromatography: SiO_2; *n*-pentane/Et_2O 3:1

yield: 111 mg (53 %)

d.r.: 94:6.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.08 (d, *J*=8.4 Hz, 2 H), 6.99 (d, *J*=8.2 Hz, 2 H), 4.30 - 4.21 (m, 1 H), 4.17 (d, *J*=14.2 Hz, 1 H), 2.92 (dd, J_1=14.2 Hz, J_2=4.3 Hz, 1 H), 2.32 (br. s., 1 H), 1.61 - 1.51 (m, 1 H), 1.44 (s, 9 H), 1.34 - 1.26 (m, 2 H), 0.99 (d, *J*=6.8 Hz, 3 H), 0.87 - 0.79 (m, 1 H).

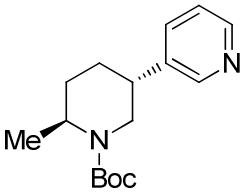
^{13}C-NMR (101 MHz, C_6D_6) δ: 155.0, 149.5, 132.3, 128.8, 126.8, 126.2, 119.4, 110.8, 79.6, 47.1, 41.4, 38.4, 28.9, 26.0, 25.6, 16.6.

MS (70 eV, EI) *m/z* (%): 300 (4) [M$^+$], 245 (13), 244 (36), 229 (64), 227 (16), 200 (12), 199 (46), 185 (36), 142 (15), 130 (10), 129 (18), 58 (20), 57 (100), 43 (52), 41 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972 (w), 2934 (w), 2228 (w), 1682 (vs), 1608 (w), 1476 (w), 1454 (w), 1414 (s), 1392 (m), 1364 (s), 1340 (m), 1308 (m), 1256 (m), 1240 (m), 1166 (s), 1148 (s), 1118 (m), 1100 (w), 1090 (m), 1052 (m), 1038 (w), 880 (w), 864 (w), 832 (m), 770 (w).

HRMS (EI) for **$C_{18}H_{24}N_2O_2$** (300.1838): 300.1831.

***trans-t*-butyl 2-methyl-5-(pyridin-3-yl)piperidine-1-carboxylate (181e)**



Cross-coupling was performed according to **TP20**.

column chromatography: SiO_2; Et_2O

yield: 116 mg (60 %)

d.r.: 95:5.

^{1}H-NMR (400 MHz, C_6D_6) δ: 8.69 (d, J=2.1 Hz, 1 H), 8.47 (dd, J_1=4.7 Hz, J_2=1.4 Hz, 1 H), 7.47 (d, J=7.8 Hz, 1 H), 6.79 (dd, J_1=7.8 Hz, J_2=4.9 Hz, 1 H), 4.31 (dd, J_1=9.8 Hz, J_2=6.3 Hz, 1 H), 4.23 (d, J=14.1 Hz, 1 H), 2.96 (dd, J_1=14.2 Hz, J_2=4.4 Hz, 1 H), 2.39 (br. s., 1 H), 1.61 - 1.52 (m, 1 H), 1.51-1.37 (m, 10 H), 1.36 - 1.29 (m, 1 H), 0.99 (d, J=6.8 Hz, 3 H), 0.88 - 0.80 (m, 1 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 155.1, 150.7, 148.3, 139.5, 134.8, 123.4, 79.5, 47.1, 41.8, 36.3, 28.9, 26.1, 25.6, 16.6.

MS (70 eV, EI) *m/z* (%): 276 (11) [M^+], 221 (19), 220 (21), 205 (24), 203 (25), 176 (43), 175 (15), 161 (75), 133 (16), 119 (27), 106 (40), 105 (17), 57 (100), 41 (15).

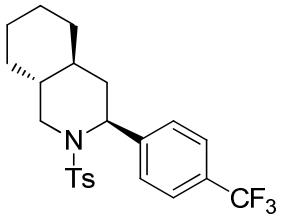
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976 (w), 2934 (w), 1680 (vs), 1476 (w), 1408 (s), 1390 (m), 1382 (m), 1364 (s), 1340 (s), 1312 (m), 1296 (w), 1256 (m), 1244 (m), 1232 (m), 1182 (m), 1172 (m), 1146 (s), 1120 (s), 1088 (s), 1048 (m), 1040 (m), 1022 (m), 1000 (m), 986 (w), 912 (w), 878 (m), 862 (m), 824 (m), 802 (m), 780 (m), 770 (s), 748 (w), 726 (w), 712 (s), 640 (m), 624 (m).

HRMS (EI) for **$C_{16}H_{24}N_2O_2$** (276.1838): 276.1834.

5.10. Typical Procedure 21: Synthesis of *N*-Tosyl Piperidines (TP 21)

To a solution of the respective *t*-butyl piperidine-1-carboxylate (Boc-protected amine) (1 equiv.) in Et_2O (3 mL per 1 mmol) was added trifluoroacetic acid (TFA; 40 equiv.) at 0 °C. The reaction mixture was stirred for 15 h at room temperature, then cooled to 0 °C and carefully neutralized using $NaHCO_3$ sat. aq. solution. The resulting mixture was extracted with CH_2Cl_2 (4 x). The combined organic phases were washed with brine and dried over Na_2SO_4. The solvents were removed via rotary evaporation. The crude deprotected amine (quant. yield) was added to a solution of *p*-tolyl-1-sulfonyl chloride (2 equiv.) and NEt_3 (2 equiv.) in THF (0.2 M). The reaction mixture was stirred for 15 h. NH_4Cl sat. aq. solution was added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x). The combined organic phases were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude product was purified via column chromatography to give the respective title compound.

2-tosyl-3-(4-(trifluoromethyl)phenyl)decahydroisoquinoline (173na)



Tosylation was performed according to **TP21**.

column chromatography: SiO_2; CH_2Cl_2

yield: 136 mg (78 %; 0.4 mmol scale)

m.p.: 194.1 – 195.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.50 (d, *J*=8.3 Hz, 2 H), 7.43 (d, *J*=8.3 Hz, 2 H), 7.39 (d, *J*=8.0 Hz, 2 H), 7.24 (d, *J*=8.0 Hz, 2 H), 4.12 (dd, J_1=11.5 Hz, J_2=3.7 Hz, 1 H), 3.91 (dd, J_1=11.3 Hz, J_2=3.6 Hz, 1 H), 2.56 - 2.37 (m, 4 H), 1.95 - 1.77 (m, 3 H), 1.73 (t, *J*=3.3 Hz, 1 H), 1.70 - 1.49 (m, 3 H), 1.47 - 1.28 (m, 2 H), 1.17 - 0.98 (m, 3 H).

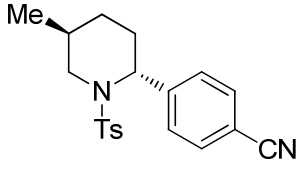
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 145.7 (d, *J*=1.3 Hz), 143.2, 134.8, 129.5, 129.2 (q, *J*=32.2 Hz), 129.1, 128.4, 128.1, 127.9, 127.8, 127.4, 124.5 (q, *J*=3.9 Hz), 124.1 (q, *J*=272.1 Hz), 63.1, 53.7, 43.6, 41.0, 40.7, 32.0, 29.9, 26.0, 25.6, 21.3.

MS (70 eV, EI) *m/z* (%): 437 (12) [M^+], 293 (17), 292 (100), 283 (14), 282 (74), 281 (44), 280 (28), 159 (19), 155 (21), 91 (36), 67 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922 (w), 2900 (w), 2846 (vw), 1600 (vw), 1446 (vw), 1426 (vw), 1344 (m), 1326 (s), 1186 (w), 1160 (vs), 1126 (s), 1106 (m), 1086 (m), 1070 (m), 1046 (w), 1034 (w), 1020 (w), 968 (w), 940 (w), 914 (w), 856 (w), 848 (w), 834 (w), 812 (w), 748 (w), 728 (m), 708 (w), 666 (w), 654 (w).

HRMS (EI) for **$C_{23}H_{26}F_3NO_2S$** (437.1636): 437.1635.

4-(*trans*-5-methyl-1-tosylpiperidin-2-yl)benzonitrile (173qa)



Tosylation was performed according to **TP21**.

column chromatography: SiO_2; CH_2Cl_2

yield: 80 mg (75 %; 0.3 mmol scale)

m.p.: 113.1 – 114.4 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.55 (d, *J*=8.2 Hz, 2 H), 7.01 (d, *J*=8.4 Hz, 2 H), 6.90 (d, *J*=8.2 Hz, 2 H), 6.77 (d, *J*=8.0 Hz, 2 H), 4.58 (t, *J*=5.0 Hz, 1 H), 3.25 (dd, J_1=12.9 Hz, J_2=3.7 Hz, 1

H), 2.98 (dd, J_1=12.9 Hz, J_2=5.3 Hz, 1 H), 1.92 (s, 3 H), 1.60 - 1.50 (m, 1 H), 1.41 - 1.31 (m, 2 H), 1.08 (dddd, J_1=13.9 Hz, J_2=9.9 Hz, J_3=4.5 Hz, J_4=4.3 Hz, 1 H), 0.71 - 0.64 (m, 1 H), 0.62 (d, J=6.9 Hz, 3 H).

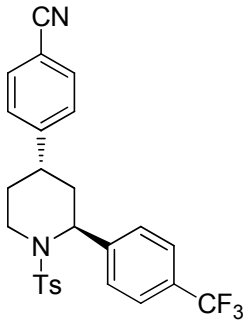
^{13}C-NMR (101 MHz, C_6D_6) δ: 146.1, 143.3, 138.3, 132.3, 129.9, 128.5, 128.0, 119.2, 111.7, 58.0, 49.6, 28.7, 27.6, 27.1, 21.5, 18.3.

MS (70 eV, EI) *m/z* (%): 354 (10) [M^+], 253 (16), 252 (100), 200 (14), 199 (99), 198 (28), 197 (49), 155 (36), 129 (26), 116 (20), 91 (53), 65 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952 (w), 2928 (w), 2226 (w), 1602 (w), 1456 (w), 1344 (s), 1320 (w), 1304 (w), 1162 (vs), 1096 (m), 1086 (m), 1068 (m), 1052 (m), 1020 (w), 1012 (m), 928 (m), 904 (m), 840 (m), 830 (m), 808 (s), 754 (w), 722 (vs), 656 (s).

HRMS (EI) for **$C_{20}H_{22}N_2O_2S$** (354.1402): 354.1398.

4-(*trans*-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzonitrile (176aa)



Tosylation was performed according to **TP21**.

column chromatography: SiO_2; ; *n*-pentane/Et_2O 2:1

yield: 174 mg (72 %; 0.5 mmol scale)

m.p.: 182.6 – 183.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, J=8.2 Hz, 2 H), 7.63 (d, J=8.2 Hz, 2 H), 7.56 (d, J=8.2 Hz, 2 H), 7.47 (d, J=8.2 Hz, 2 H), 7.37 (d, J=8.0 Hz, 2 H), 7.10 (d, J=8.2 Hz, 2 H), 5.52 (d, J=3.5 Hz, 1 H), 4.08 (d, J=14.2 Hz, 1 H), 3.17 - 3.08 (m, 1 H), 2.73 - 2.64 (m, 1 H), 2.49 (s, 3 H), 2.41 (d, J=13.5 Hz, 1 H), 1.91 (td, J_1=13.5 Hz, J_2=5.5 Hz, 1 H), 1.63 (d, J=12.9 Hz, 1 H), 1.51 (qd, J_1=12.7 Hz, J_2=4.5 Hz, 1 H).

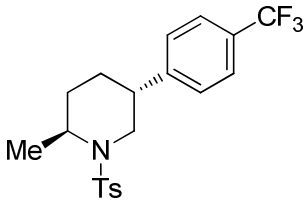
^{13}C-NMR (101 MHz, $CDCl_3$) δ: 149.9, 143.7, 142.5 (d, J=0.8 Hz), 138.0, 132.5, 129.9, 129.6 (q, J=32.6 Hz), 127.4, 127.0, 127.0, 125.9 (q, J=3.7 Hz), 124.0 (q, J=272.1 Hz), 118.6, 110.7, 55.0, 41.6, 36.8, 34.1, 31.3, 21.5.

MS (70 eV, EI) *m/z* (%): 484 (11) [M^+], 339 (43), 330 (25), 329 (100), 328 (24), 327 (12), 186 (23), 172 (12), 159 (11), 155 (15), 90 (30).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2956 (vw), 2932 (w), 2232 (w), 1606 (w), 1598 (w), 1506 (vw), 1452 (w), 1434 (w), 1412 (w), 1376 (w), 1348 (w),1328 (vs), 1290 (m), 1256 (w), 1196 (w), 1158 (vs), 1110 (vs), 1096 (s), 1072 (s), 1034 (w), 1018 (m), 944 (m), 928 (m), 906 (m), 838 (s), 802 (w), 738 (w), 716 (m), 702 (m), 664 (s), 650 (m), 634 (w).

HRMS (EI) for **$C_{26}H_{23}F_3N_2O_2S$** (484.1432): 484.1439.

***trans*-2-methyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)-piperidine (181ca)**



Tosylation was performed according to **TP21**.

column chromatography: SiO_2; CH_2Cl_2

yield: 145 mg (73 %; 0.5 mmol scale)

m.p.: 133.0 – 135.9 °C.

^{1}H-NMR (599 MHz, C_6D_6) δ: 7.63 (d, J=8.2 Hz, 2 H), 7.31 (d, J=8.0 Hz, 2 H), 7.04 (d, J=8.2 Hz, 2 H), 6.77 (d, J=8.0 Hz, 2 H), 3.59 - 3.52 (m, 1 H), 3.43 (dd, J_1=12.6 Hz, J_2=3.8 Hz, 1 H), 3.27 (dd, J_1=12.6 Hz, J_2=5.5 Hz, 1 H), 2.51 - 2.44 (m, 1 H), 1.91 (s, 3 H), 1.48 - 1.43 (m, 1 H), 1.42 - 1.36 (m, 1 H), 1.16 (dddd, J_1=13.2 Hz, J_2=6.5 Hz, J_3=6.4 Hz, J_4=3.3 Hz, 1 H), 1.01 - 0.97 (m, 1 H) 1.02 (d, J=6.6 Hz, 3 H).

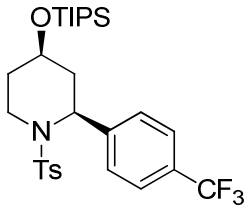
^{13}C-NMR (151 MHz, $CDCl_3$) δ: 147.7 (d, J=1.1 Hz), 143.1, 138.4, 129.9, 129.1 (q, J=32.0 Hz), 128.7, 128.1, 125.8 (q, J=3.8 Hz), 125.5 (q, J=271.8 Hz), 51.5, 47.8, 39.4, 30.1, 26.8, 21.4, 17.3.

MS (70 eV, EI) *m/z* (%): 397 (2) [M^+], 383 (19), 382 (100), 155 (18), 91 (12).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2940 (w), 2926 (w), 1686 (w), 1446 (w), 1384 (w), 1322 (s), 1300 (m), 1288 (m), 1264 (m), 1238 (m), 1196 (m), 1180 (m), 1154 (s), 1112 (vs), 1094 (s), 1082 (s), 1066 (s), 1042 (m), 1016 (m), 994 (m), 978 (m), 966 (s), 960 (m), 908 (m), 872 (m), 840 (m), 820 (s), 738 (w), 710 (s), 684 (s), 646 (s), 632 (m), 606 (m).

HRMS (EI) for **$C_{20}H_{22}F_3NO_2S$** (397.1323): 397.1320.

***cis*-1-tosyl-2-(4-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)piperidine**



Tosylation was performed according to **TP21**.

column chromatography: SiO_2; *n*-pentane/Et_2O 10:1

yield: 6.22 g (56 %; 20 mmol scale)

m.p.: 93.8 – 95.3 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.68 (d, *J*=8.2 Hz, 2 H), 7.29 (d, *J*=8.2 Hz, 2 H), 7.14 (d, *J*=8.0 Hz, 2 H), 6.79 (d, *J*=8.0 Hz, 2 H), 5.19 (d, *J*=2.9 Hz, 1 H), 3.71 (dt, J_1=13.9 Hz, J_2=3.8 Hz, 1 H), 3.62 (br. s., 1 H), 3.55 - 3.47 (m, 1 H), 1.97 - 1.93 (m, 1 H), 1.93 (s, 3 H), 1.65 (ddd, J_1=14.2 Hz, J_2=6.6 Hz, J_3=2.9 Hz, 1 H), 1.45 - 1.36 (m, 1 H), 1.26 - 1.19 (m, 1 H), 0.97 - 0.73 (m, 18 H), 0.70 - 0.59 (m, 3 H).

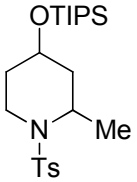
^{13}C-NMR (101 MHz, C_6D_6) δ: 146.5 (d, *J*=1.1 Hz), 143.2, 139.7, 130.0, 129.1 (q, *J*=32.2 Hz), 127.8, 127.4, 125.6 (q, *J*=3.8 Hz), 125.4 (d, *J*=271.8 Hz), 65.4, 54.8, 38.3, 37.4, 32.6, 21.4, 18.4, 18.4, 12.6.

MS (70 eV) *m/z* (%): 514 (13), 513 (34), 512 (100), 314 (14), 310 (44), 298 (40), 296 (15), 284 (24), 272 (10), 242 (20), 159 (25), 157 (11), 155 (26); 129 (16); 101 (12); 91 (59); 87 (11); 75 (20), 61 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2938 (w), 2866 (w), 1326 (vs), 1312 (s), 1302 (m), 1162 (s), 1156 (s), 1124 (vs), 1110 (s), 1080 (s), 1070 (s), 1058 (m), 1036 (m), 1016 (s), 950 (m), 936 (s), 936 (s), 898 (m), 882 (m), 820 (m), 746 (m), 716 (s), 688 (s), 678 (s), 658 (s), 650 (s), 630 (m).

HRMS (ESI) for **$C_{28}H_{41}F_3NO_3SSi^+$** (556.2523) [M+H$^+$]: 556.2524.

2-methyl-1-tosyl-4-((triisopropylsilyl)oxy)piperidine



Tosylation was performed according to **TP21**.

column chromatography: SiO_2; CH_2Cl_2

yield: 2.77 g (65 %; 10 mmol scale)

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.80 (d, *J*=8.3 Hz, 2 H), 6.82 (d, *J*=8.0 Hz, 2 H), 4.29 - 4.18 (m, 1 H), 3.74 - 3.63 (m, 2 H), 3.48 - 3.37 (m, 1 H), 1.91 (s, 3 H), 1.56 - 1.43 (m, 2 H), 1.42 - 1.34 (m, 2 H), 1.31 (d, *J*=7.2 Hz, 3 H), 1.08 - 0.92 (m, 18 H), 0.92 - 0.86 (m, 3 H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 142.7, 140.4, 130.0, 127.8, 65.9, 48.8, 37.9, 36.3, 33.6, 21.5, 19.9, 18.6, 12.7.

MS (70 eV, EI) *m/z* (%): 424 (1), 384 (12), 383 (26), 382 (100), 90 (12).

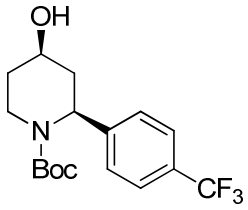
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942 (m), 2890 (m), 2866 (m), 1598 (vw), 1494 (w), 1464 (m), 1380 (w), 1346 (m), 1328 (m), 1250 (w), 1216 (w), 1162 (vs), 1130 (s), 1106 (m), 1088 (m), 1060 (s), 1040 (s), 1018 (m), 988 (m), 966 (vs), 914 (s), 882 (s), 870 (s), 814 (m), 776 (m), 712 (s), 700 (s), 678 (vs), 654 (s), 642 (s).

HRMS (EI) for **$C_{21}H_{36}NO_3SSi^+$** (410.2185) $[M\text{-}CH_3]^+$: 410.2207.

5.11. Typical Procedure 22: TIPS Deprotection (TP 22)

To a solution of the respective 4-((triisopropylsilyl)oxy)piperidine (1 equiv.) in THF (0.2 M) was added *n*-$Bu_4NF \cdot 3\ H_2O$ (2 equiv.) portionwise. The reaction mixture was stirred for 15 h at room temperature, then H_2O was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude product was subjected to column chromatography.

***t*-butyl *cis*-2-(4-fluorophenyl)-4-hydroxypiperidine-1-carboxylate**



Desilylation was performed according to **TP22**.

column chromatography: SiO_2; CH_2Cl_2/acetone 7:1

yield: 1.54 g (89 %; 5 mmol scale)

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.37 (d, *J*=8.3 Hz, 2 H), 7.09 (d, *J*=8.3 Hz, 2 H), 5.17 (br. s., 1 H), 3.98 (ddd, J_1=13.6 Hz, J_2=5.0 Hz, J_3=2.8 Hz, 1 H), 3.60 - 3.48 (m, 1 H), 3.20 (td, J_1=12.9 Hz, J_2=3.5 Hz, 1 H), 1.85 - 1.72 (m, 1 H), 1.61 (ddd, J_1=14.4 Hz, J_2=6.8 Hz, J_3=3.2 Hz, 1 H), 1.53 - 1.41 (m, 1 H), 1.36 (s, 9 H), 1.28 - 1.14 (m, 1 H).

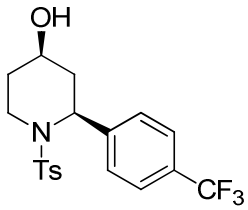
^{13}C-NMR (75 MHz, C_6D_6) δ: 155.0, 147.3 (d, *J*=1.1 Hz), 128.2 (q, *J*=32.3 Hz), 126.1, 124.8 (q, *J*=271.8 Hz), 125.0 (q, *J*=3.6 Hz), 79.3, 63.9, 52.2, 35.6, 35.5, 31.9, 27.9.

MS (70 eV, EI) *m/z* (%): 345 (0.3) [M^+], 290 (12), 289 (68), 270 (11), 244 (40), 228 (11), 200 (18), 186 (11), 172 (15), 59 (100), 41 (13), 18 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3438 (w), 2978 (w), 2932 (w), 1664 (s), 1620 (w), 1478 (w), 1454 (w), 1416 (m), 1394 (m), 1366 (m), 1324 (vs), 1280 (m), 1252 (m), 1210 (w), 1160 (s), 1112 (vs), 1068 (vs), 1040 (s), 1016 (m), 988 (w), 970 (w), 958 (w), 940 (m), 862 (m), 838 (m), 830 (m), 774 (w), 760 (w).

HRMS (EI) for **$C_{17}H_{22}F_3NO_3$** (345.1552): 345.1562.

***cis*- 1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-ol**



Desilylation was performed according to **TP22**.

column chromatography: SiO_2; CH_2Cl_2/acetone 10:1 to 5:1

yield: 3.48 g (87 %; 10 mmol scale)

m.p.: 114.0 – 115.5 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ: 7.50 (d, *J*=8.2 Hz, 2 H), 7.21 (d, *J*=8.4 Hz, 2 H), 7.07 (d, *J*=8.2 Hz, 2 H), 6.68 (d, *J*=7.9 Hz, 2 H), 4.85 (t, *J*=4.7 Hz, 1 H), 3.51 - 3.42 (m, 1 H), 3.40 - 3.30 (m, 1 H), 3.26 (br. s., 1 H), 1.89 - 1.80 (m, 3 H), 1.64 (dt, J_1=14.3 Hz, J_2=4.1 Hz, 1 H), 1.47 (ddd, *J*=14.3 Hz, J_2=6.2 Hz, J_3=3.3 Hz, 1 H), 1.36 - 1.28 (m, 1 H), 1.06 - 0.99 (m, 1 H).

^{13}C-NMR (101 MHz, C_6D_6) δ: 146.0 (d, *J*=1.2 Hz), 143.2, 139.2, 130.0, 129.3 (q, *J*=32.2 Hz), 127.8, 127.8, 125.5 (q, *J*=3.9 Hz), 125.4 (q, *J*=271.3 Hz), 64.6, 55.4, 38.9, 36.6, 32.1, 21.4.

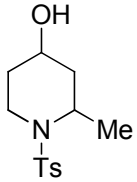
^{19}F-NMR (376 MHz, C_6D_6) δ: -62.10 (s) (major), -62.25 (s) (minor).

MS (70 eV) *m/z* (%): 399 (1) [M^+], 254 (41), 245 (16), 244 (100), 243 (13), 242 (40), 226 (35), 200 (12), 199 (13), 172 (25), 159 (19), 155 (32), 91 (61); 65 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2938 (w), 1622 (w), 1598 (w), 1456 (w), 1426 (w), 1326 (vs), 1260 (w), 1162 (vs), 1116 (s), 1096 (m), 1068 (s), 1046 (s), 1020 (m), 982 (m), 932 (m), 854 (m), 832 (m), 814 (s), 720 (s), 706 (m), 654 (s).

HRMS (ESI) for **$C_{19}H_{21}F_3NO_3S^+$** (400.1189) [M+H^+]: 400.1189.

2-methyl-1-tosylpiperidin-4-ol



Desilylation was performed according to **TP22**.

column chromatography: SiO_2; *n*-pentane/Et_2O 5:1 to Et_2O (neat)

yield: 1.38 g (73 %; 7 mmol scale)

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.73 (d, *J*=8.0 Hz, 2 H), 6.80 (d, *J*=8.0 Hz, 2 H), 4.13 - 3.98 (m, 1 H), 3.60 - 3.29 (m, 3 H), 1.91 (s, 3 H), 1.53 - 1.33 (m, 2 H), 1.23 (d, *J*=6.9 Hz, 3 H), 1.17 (d, *J*=3.6 Hz, 2 H), 1.01 - 0.90 (m, 1 H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 142.8, 140.0, 130.0, 127.8, 64.8, 48.9, 37.6, 36.7, 32.9, 21.5, 19.6.

MS (70 eV, EI) *m/z* (%): 269 (3) [M^+], 255 (14), 254 (100), 210 (9), 155 (26), 90 (38).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3516 (w), 2924 (w), 2882 (w), 1598 (w), 1494 (w), 1454 (w), 1424 (w), 1402 (w), 1382 (w), 1366 (w), 1344 (m), 1322 (m), 1304 (m), 1288 (m), 1234 (w), 1216 (w), 1184 (w), 1158 (s), 1148 (s), 1132 (s), 1098 (m), 1080 (s), 1056 (m), 1038 (m), 1018 (m), 1008 (w), 982 (m), 942 (m), 912 (s), 890 (w), 852 (m), 814 (m), 788 (w), 732 (w), 710 (s), 688 (vs), 642 (s).

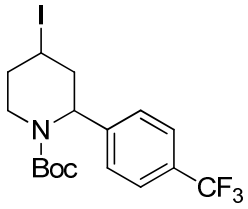
HRMS (EI) for **$C_{13}H_{19}NO_3S$** (269.1086): 269.1078.

5.12. Typical Procedure 23: Iodination[85] (TP 23)

In a dry and Ar-flushed Schlenk-flask I_2 (1.2 equiv.) was dissolved in CH_2Cl_2 (0.6 M). The solution was cooled to 0 °C and PPh_3 (1.2 equiv.) was added portionwise. The resulting yellow suspension was stirred for 1 h 30 min at 0 °C before *N*-methyl-imidazole (NMI; 1.25 equiv.) was added. The respective piperidin-4-ol (1 equiv.) was transferred drop- or portionwise to this mixture. The reaction mixture was allowed to proceed for 6 h at 0 °C, then quenched with $NaHSO_3$ sat. aq. solution. Phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). Solvents were evaporated and the crude product was subjected to column chromatography.

[85] Lange, G. L. & Gottardo, C. Facile conversion of primary and secondary alcohols to alkyl iodides. *Synth. Commun.* **20**, 1473-1479 (1990).

_t_-butyl 4-iodo-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (175a)



Iodination was performed according to **TP23**.

column chromatography: SiO_2; *n*-pentane/Et_2O 7:1

yield: 2.17 g (68 %; 7 mmol scale)

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.26 (d, *J*=8.3 Hz, 2 H), 6.78 (d, *J*=8.3 Hz, 2 H), 5.22 (br. s., 1 H), 3.76 (d, *J*=13.0 Hz, 1 H), 3.53 (tt, J_1=12.4 Hz, J_2=3.9 Hz, 1 H), 2.50 (dt, J_1=13.6 Hz, J_2=1.8 Hz, 1 H), 2.26 - 2.07 (m, 2 H), 1.82 (qd, J_1=12.4 Hz, J_2=4.4 Hz, 1 H), 1.72 - 1.61 (m, 1 H), 1.41 (s, 9 H).

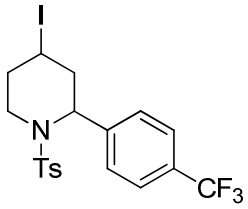
^{13}C-NMR (75 MHz, C_6D_6) δ: 155.3, 143.6 (d, *J*=1.1 Hz), 129.6 (q, *J*=32.3 Hz), 129.0, 127.2, 126.3 (q, *J*=3.9 Hz), 125.4, 125.2 (q, *J*=272.1 Hz), 80.4, 56.1, 42.4, 41.7, 39.6, 28.7, 20.3.

MS (70 eV, EI) *m/z* (%): 455 (1) [M^+], 399 (22), 328 (12), 272 (49), 228 (42), 199 (18), 159 (16), 61 (13), 59 (100), 41 (13), 18 (38).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2974 (w), 2932 (w), 2870 VW 1690 (s), 1620 (w), 1478 (w), 1452 (w), 1412 (s), 1366 (m), 1324 (vs), 1264 (m), 1248 (m), 1154 (vs), 1122 (vs), 1068 (s), 1014 (m), 1004 (m), 982 (m), 954 (w), 910 (m), 870 (w),852 (m), 836 (m), 794 (w), 772 (m), 732 (w), 722 (w), 642 (w).

HRMS (EI) for **$C_{17}H_{21}F_3INO_2$** (455.0569): 455.0561.

4-iodo-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidine (175b)



Iodination was performed according to **TP23**.

column chromatography: SiO_2; *n*-pentane/Et_2O 10:1

yield: 2.24 g (55 %; 8 mmol scale)

m.p.: 132.6 – 133.8 °C.

^{1}H-NMR (400 MHz, C_6D_6) δ:7.64 (d, *J*=8.2 Hz, 2 H), 7.25 (d, *J*=8.4 Hz, 2 H), 6.95 (d, *J*=8.2 Hz, 2 H), 6.78 (d, *J*=7.9 Hz, 2 H), 4.98 (d, *J*=2.9 Hz, 1 H), 3.51 - 3.38 (m, 2 H), 2.46 - 2.29

(m, 2 H), 1.99 (td, J_1=13.4 Hz, J_2=5.4 Hz, 1 H), 1.89 (s, 3 H), 1.66 (qd, J_1=12.6 Hz, J_2=4.6 Hz, 1 H), 1.50 - 1.43 (m, 1 H).

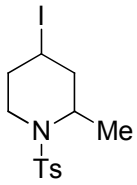
^{13}C-NMR (101 MHz, C_6D_6) δ: 143.8, 142.4 (d, J=1.2 Hz), 139.3, 130.3, 129.9 (q, J=32.3 Hz), 127.8, 127.6, 126.4 (q, J=3.7 Hz), 125.2 (q, J=272.0 Hz), 57.9, 43.7, 40.8, 38.3, 21.5, 19.0.

MS (70 eV) *m/z* (%): 509 (1) [M^+], 383 (22), 382 (100), 226 (12), 199 (63), 186 (23), 185 (10), 184 (53), 159 (54), 155 (87), 91 (67), 65 (11), 55 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1326 (vs), 1292 (m), 1154 (s), 1118 (s), 1102 (m), 1090 (s), 1070 (s), 1058 (s), 1044 (m), 1016 (m), 998 (m), 954 (s), 930 (s), 906 (m), 854 (m), 844 (m), 828 (m), 816 (s), 742 (m), 710 (s), 694 (s), 652 (vs).

HRMS (ESI) for **$C_{19}H_{19}F_3INO_2SCl^-$** (543.9827) [M+$Cl^-$]:543.9817.

2-methyl-4-iodo-1-tosylpiperidine (175c)



Iodination was performed according to **TP23**.

column chromatography: SiO_2; CH_2Cl_2

yield: 1.12 g (59 %; 5 mmol scale)

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.63 (d, J=8.3 Hz, 2 H), 6.77 (d, J=8.0 Hz, 2 H), 4.00 - 3.84 (m, 1 H), 3.67 (tt, J_1=12.3 Hz, J_2=4.4 Hz, 1 H), 3.38 (dt, J_1=13.8 Hz, J_2=1.7 Hz, 1 H), 2.41 (ddd, J_1=13.7 Hz, J_2=12.2 Hz, J_3=3.2 Hz, 1 H), 1.99 - 1.90 (m, 1 H), 1.88 (s, 3 H), 1.81 - 1.67 (m, 1 H), 1.67 - 1.57 (m, 2 H), 0.58 (d, J=6.9 Hz, 3 H).

^{13}C-NMR (75 MHz, C_6D_6) δ: 143.1, 139.6, 130.1, 127.7, 51.4, 44.3, 42.2, 39.2, 21.5, 20.1, 15.5.

MS (70 eV, EI) *m/z* (%): 379 (1) [M^+], 363 (12), 253 (15), 252 (100), 155 (51), 90 (61), 69 (10), 66 (10), 58 (17), 56 (12).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2974 (w), 2924 (w), 2870 (vw), 1598 (w), 1494 (vw), 1444 (w), 1380 (w), 1330 (s), 1302 (m), 1258 (m), 1204 (w), 1178 (m), 1150 (vs), 1092 (s), 1070 (m), 1056 (m), 1018 (w), 1008 (m), 988 (s), 964 (w), 914 (s), 878 (w), 852 (m), 814 (s), 724 (w), 708 (m), 684 (vs), 644 (s).

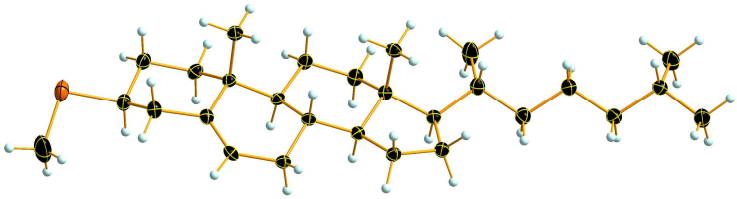
HRMS (EI) for **$C_{13}H_{18}INO_2S$** (379.0103): 379.0118.

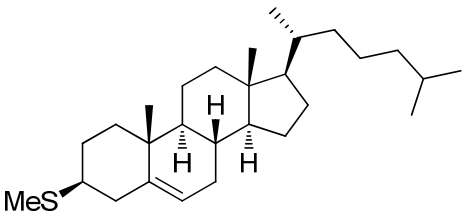
D. Appendix

1. Data of X-ray Analysis

1.1. Stereoselective Preparation, Configurational Stability and Reactivity of Substituted Cyclohexyllithium Derivatives

(*β*-cholesteryl)(methyl)sulfane (*β-(eq)*-94a) (Table 2)



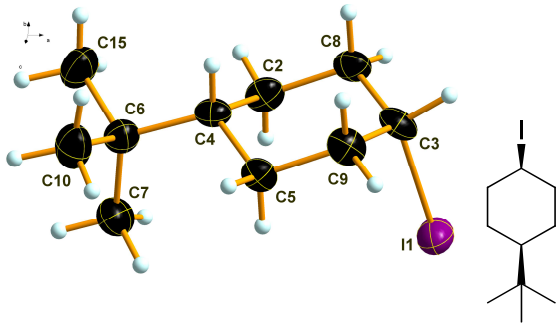


Crystal Data

net formula	$C_{28}H_{48}S$
M_r	416.73
T[K]	100(2)
Colour, habit	colorless block
Cryst. size, mm^2	0.30 × 0.20 × 0.15
Crystal system	monoclinic
Space group	*P*21 (No. 4)
a [Å]	12.7859(5)
b [Å]	8.6507(3)
c [Å]	13.0257(6)
α [°]	90.0
β [°]	118.159(4)
γ [°]	90.0
V [Å^3]	1270.21(10)
Z	2
ρ_{calcd} [g cm^{-3}]	1.090
μ [mm^{-1}]	0.139
F(000)	464
hkl range	$-15 \le h \le 15$
	$-10 \le k \le 10$
	$-16 \le l \le 16$
Reflns. collected	12916
Reflns. obsd.	4682
Reflns. unique	4976

R_{int}	0.0251
Param. refined	262
θ range [°]	4.26 - 26.00
$R1$, wR_2 [I > 2σ(I)]	0.0343, 0.0870
$R1$, wR_2 (all data)	0.0374, 0.0889
GooF	1.033
Peak / hole [e Å^3]	0.282, -0.161

cis-1-(_tert_-butyl)-4-iodocyclohexane (_cis-(ax)_-78) (Scheme 28)

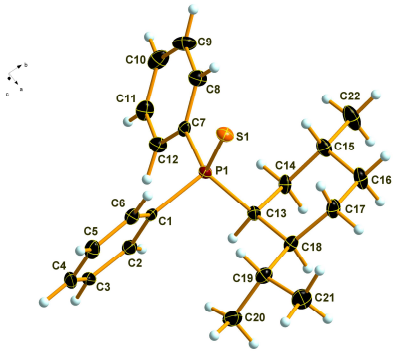


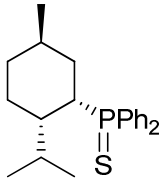
Crystal Data

Formula	$C_{10}H_{19}I$
M_r	266.15
T[K]	173(2)
Colour, habit	colorless block
Cryst. size, mm^2	0.35 × 0.25 × 0.08
Crystal system	monoclinic
Space group	$P21/c$
a [Å]	17.8172(9)
b [Å]	6.0632(3)
c [Å]	10.7371(5)
α [°]	90.0
β [°]	104.538(4)
γ [°]	90.0
V [Å^3]	1122.78(10)
Z	4
ρ_{calcd} [g cm^{-3}]	1.575
μ [mm^{-1}]	2.799
F(000)	528
hkl range	$-21 \leq h \leq 21$
	$-7 \leq k \leq 7$
	$-12 \leq l \leq 12$
Reflns. collected	9572
Reflns. obsd.	1708
Reflns. unique	1972
R_{int}	0.0386
Param. refined	172
θ range [°]	4.11 - 25.00
$R1$, wR_2 [I > 2σ(I)]	0.0255, 0.0635
$R1$, wR_2 (all data)	0.0326, 0.0675

GooF	1.072
Peak / hole [e Å^3]	0.905, -0.437

((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)diphenylphosphine sulfide (*neomen-(ax)*-91b) (Table 3)

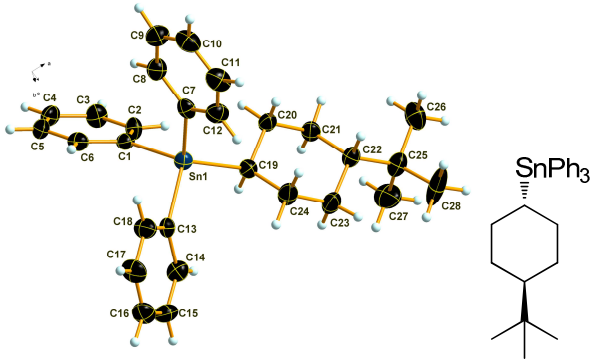




Crystal Data

Formula	$C_{22}H_{29}PS$
M_r	356.48
T[K]	100(2)
Colour, habit	colorless block
Cryst. size, mm^2	0.20 × 0.10 × 0.10
Crystal system	orthorhombic
Space group	*P*212121
a [Å]	7.6548(3)
b [Å]	14.5175(5)
c [Å]	18.1211(7)
α [°]	90.0
β [°]	90.0
γ [°]	90.0
V [Å^3]	2013.77(13)
Z	4
ρ_{calcd} [g cm^{-3}]	1.176
μ [mm^{-1}]	0.241
F(000)	768
hkl range	$-9 \le h \le 9$
	$-17 \le k \le 17$
	$-21 \le l \le 21$
Reflns. collected	18801
Reflns. obsd.	3358
Reflns. unique	3517
R_{int}	0.0400
Param. refined	313
θ range [°]	4.30 - 25.00
*R*1, *wR*$_2$ [I > 2σ(*I*)]	0.0262, 0.0612
*R*1, *wR*$_2$ (all data)	0.0284, 0.0622
GooF	1.067
Peak / hole [e Å^3]	0.243, -0.178

(*trans*-4-(*tert*-butyl)cyclohexyl)triphenylstannane (*trans-(eq)*-82f) (Table 1)

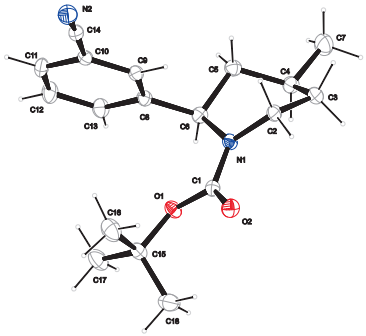


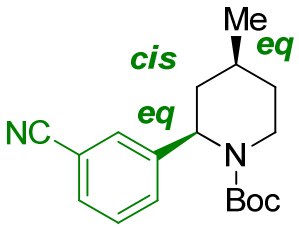
Crystal Data

Formula	$C_{28}H_{34}Sn$
M_r	489.24
T[K]	173(2)
Colour, habit	colorless needle
Cryst. size, mm^2	0.30 × 0.10 × 0.05
Crystal system	monoclinic
Space group	*P*21/*n*
a [Å]	6.9567(4)
b [Å]	12.1094(5)
c [Å]	29.0071(12)
α [°]	90.0
β [°]	94.261(4)
γ [°]	90.0
V [$Å^3$]	2436.8(2)
Z	4
ρ_{calcd} [g cm^{-3}]	1.334
μ [mm^{-1}]	1.059
F(000)	1008
hkl range	$-8 \leq h \leq 8$
	$-14 \leq k \leq 11$
	$-34 \leq l \leq 34$
Reflns. collected	11403
Reflns. obsd.	3631
Reflns. unique	4270
R_{int}	0.0343
Param. refined	362
θ range [°]	4.10 - 25.00
*R*1, wR_2 [I > 2σ(*I*)]	0.0283, 0.0618
*R*1, wR_2 (all data)	0.0369, 0.0649
GooF	1.023
Peak / hole [e $Å^3$]	0.751, -0.298

1.2. Highly Diastereoselective Arylations of Substituted Piperidines

cis-*t*-butyl 2-(3-cyanophenyl)-4-methylpiperidine-1-carboxylate (173d)



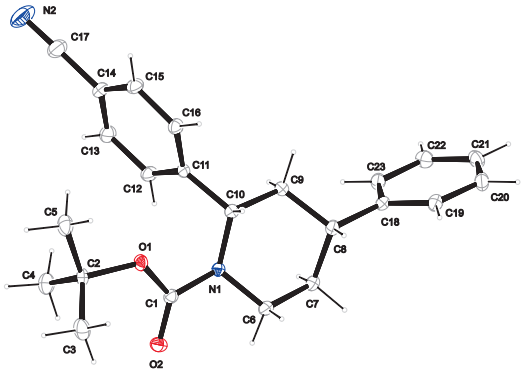


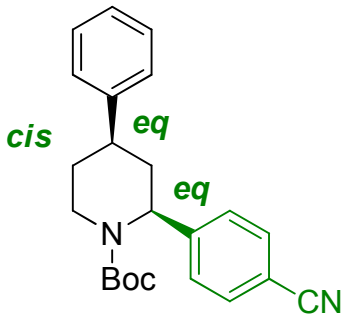
Crystal Data

net formula	$C_{18}H_{24}N_2O_2$
M_r/g mol^{-1}	300.395
crystal size/mm	0.60 × 0.13 × 0.07
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	6.3135(4)
b/Å	10.2813(10)
c/Å	13.8719(10)
α/°	76.283(7)
β/°	85.876(6)
γ/°	77.838(7)
V/Å^3	854.90(12)
Z	2
calc. density/g cm^{-3}	1.16698(16)
μ/mm^{-1}	0.076
absorption correction	'multi-scan'
transmission factor range	0.72269–1.00000
refls. measured	5884
R_{int}	0.0355
mean σ(I)/I	0.0856
θ range	4.24–26.33
observed refls.	1872
x, y (weighting scheme)	0.0371, 0
hydrogen refinement	constr
refls in refinement	3435
parameters	203
restraints	0
$R(F_{obs})$	0.0427
$R_w(F^2)$	0.0891
S	0.830
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.163

min electron density/e Å^{-3}	−0.141

cis-t-butyl 2-(3-cyanophenyl)-4-phenylpiperidine-1-carboxylate (173h)



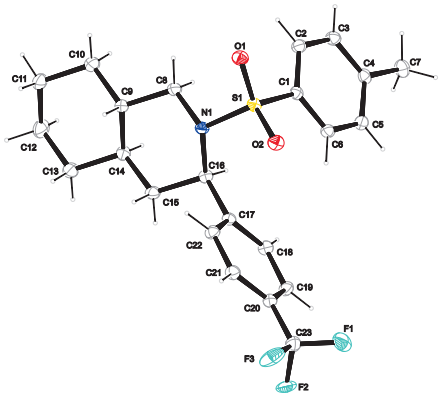


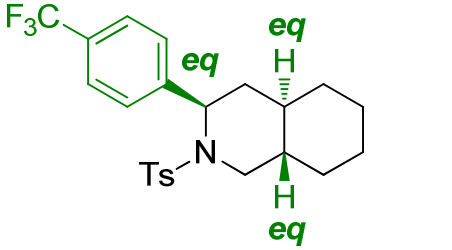
Crystal Data

net formula	$C_{23}H_{26}N_2O_2$
M_r/g mol^{-1}	362.465
crystal size/mm	0.39 × 0.22 × 0.12
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1/c$
a/Å	14.5171(9)
b/Å	11.6682(8)
c/Å	12.0141(8)
α/°	90
β/°	98.276(7)
γ/°	90
V/Å^3	2013.9(2)
Z	4
calc. density/g cm^{-3}	1.19548(12)
μ/mm^{-1}	0.076
absorption correction	'multi-scan'
transmission factor range	0.96746–1.00000
refls. measured	8788
R_{int}	0.0314
mean σ(I)/I	0.0756
θ range	4.23–26.32
observed refls.	2310
x, y (weighting scheme)	0.0279, 0
hydrogen refinement	constr
refls in refinement	4068
parameters	247
restraints	0
$R(F_{obs})$	0.0351
$R_w(F^2)$	0.0680
S	0.806
shift/error$_{max}$	0.001

max electron density/e Å^{-3}	0.156
min electron density/e Å^{-3}	−0.144

2-tosyl-3-(4-(trifluoromethyl)phenyl)decahydroisoquinoline (173na)





(from Boc-protected piperidine)

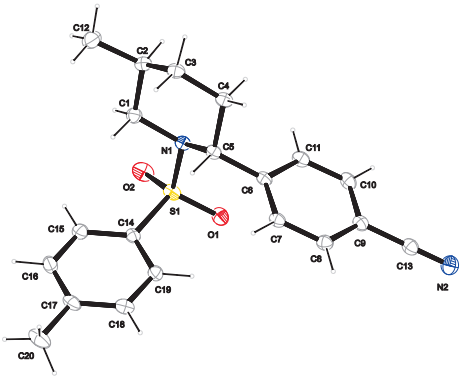
Crystal Data

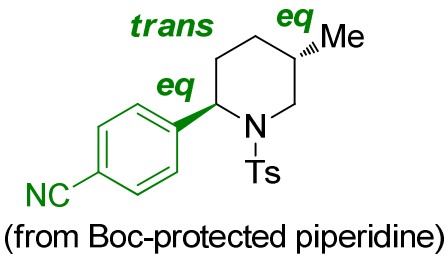
net formula	$C_{23}H_{26}F_3NO_2S$
M_r/g mol^{-1}	437.519
crystal size/mm	0.51 × 0.05 × 0.02
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	*C*2/*c*
a/Å	31.5413(5)
b/Å	5.49050(10)
c/Å	25.8592(4)
α/°	90
β/°	110.7934(8)
γ/°	90
V/Å^3	4186.55(12)
Z	8
calc. density/g cm^{-3}	1.38831(4)
μ/mm^{-1}	0.201
absorption correction	none
refls. measured	12910
R_{int}	0.0338
mean σ(I)/I	0.0306
θ range	3.37–25.36
observed refls.	3115
x, y (weighting scheme)	0.0296, 5.6059
hydrogen refinement	constr
refls in refinement	3826
parameters	300
restraints	0
$R(F_{obs})$	0.0383
$R_w(F^2)$	0.0938
S	1.088
shift/error$_{max}$	0.001

max electron density/e Å^{-3}	0.223
min electron density/e Å^{-3}	−0.367

F atoms disordered, split model applied, sof ratio about 1:1.

4-(*cis*-5-methyl-1-tosylpiperidin-2-yl)benzonitrile (173qa)





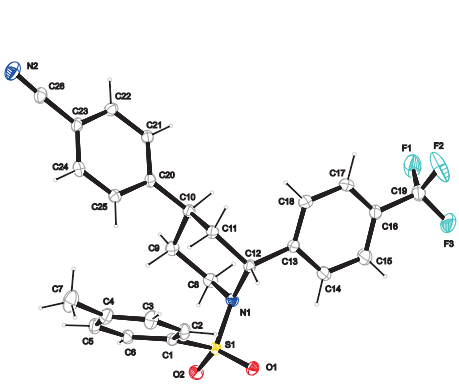
(from Boc-protected piperidine)

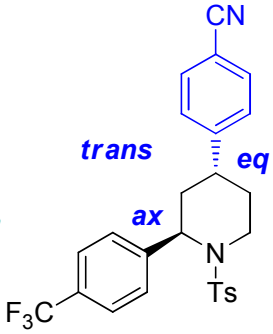
Crystal Data

net formula	$C_{20}H_{22}N_2O_2S$
M_r/g mol^{-1}	354.467
crystal size/mm	0.40 × 0.08 × 0.05
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	5.4884(2)
b/Å	11.8978(8)
c/Å	14.2002(7)
α/°	77.357(5)
β/°	86.323(4)
γ/°	87.651(4)
V/Å^3	902.58(8)
Z	2
calc. density/g cm^{-3}	1.30429(12)
μ/mm^{-1}	0.195
absorption correction	'multi-scan'
transmission factor range	0.98356–1.00000
refls. measured	6364
R_{int}	0.0211
mean σ(I)/I	0.0554
θ range	4.36–26.34
observed refls.	2403
x, y (weighting scheme)	0.0431, 0
hydrogen refinement	constr
refls in refinement	3645
parameters	228
restraints	0
$R(F_{obs})$	0.0371

$R_w(F^2)$	0.0847
S	0.886
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.209
min electron density/e Å^{-3}	−0.269

4-(*trans*-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidin-4-yl)benzonitrile (176aa)





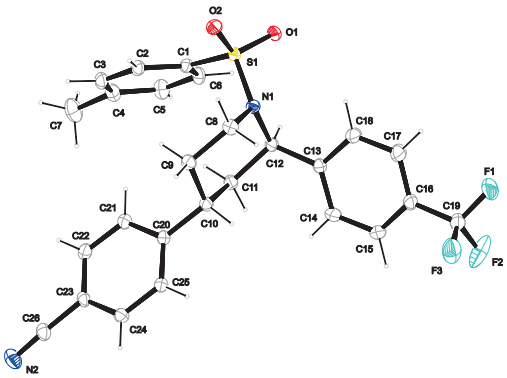
(from Boc-protected piperidine)

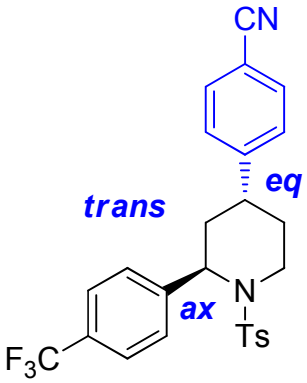
Crystal Data

net formula	$C_{26}H_{23}F_3N_2O_2S$
M_r/g mol^{-1}	484.534
crystal size/mm	0.35 × 0.04 × 0.04
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	*C*2/*c*
a/Å	22.4013(9)
b/Å	14.5197(5)
c/Å	15.9116(7)
α/°	90
β/°	116.2671(19)
γ/°	90
V/Å^3	4641.0(3)
Z	8
calc. density/g cm^{-3}	1.38694(9)
μ/mm^{-1}	0.190
absorption correction	none
refls. measured	14235
R_{int}	0.0717
mean σ(I)/I	0.0550
θ range	3.15–25.34
observed refls.	2969
x, y (weighting scheme)	0.0316, 6.9720
hydrogen refinement	constr
refls in refinement	4228
parameters	308
restraints	0
$R(F_{obs})$	0.0448

$R_w(F^2)$	0.1096
S	1.009
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.298
min electron density/e Å^{-3}	−0.337

4-(*trans*-1-tosyl-2-(4-(trifluoro-methyl)phenyl)-piperidin-4-yl)benzonitrile (176c)



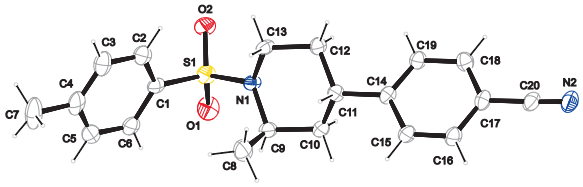


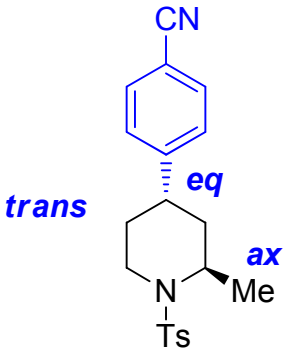
Crystal Data

net formula	$C_{26}H_{23}F_3N_2O_2S$
M_r/g mol^{-1}	484.534
crystal size/mm	0.21 × 0.15 × 0.096
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$C2/c$
a/Å	22.3664(8)
b/Å	14.5275(6)
c/Å	15.9004(5)
α/°	90
β/°	116.2098(18)
γ/°	90
V/Å^3	4635.3(3)
Z	8
calc. density/g cm^{-3}	1.38865(9)
μ/mm^{-1}	0.191
absorption correction	none
refls. measured	10097
R_{int}	0.0369
mean σ(I)/I	0.0542
θ range	3.15–27.49
observed refls.	3351
x, y (weighting scheme)	0.0577, 3.2402
hydrogen refinement	constr
refls in refinement	5236
parameters	308
restraints	0
$R(F_{obs})$	0.0484

$R_w(F^2)$	0.1319
S	1.037
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.361
min electron density/e Å^{-3}	−0.378

4-(*trans*-2-methyl-1-tosylpiperidin-4-yl)benzonitrile (176e)





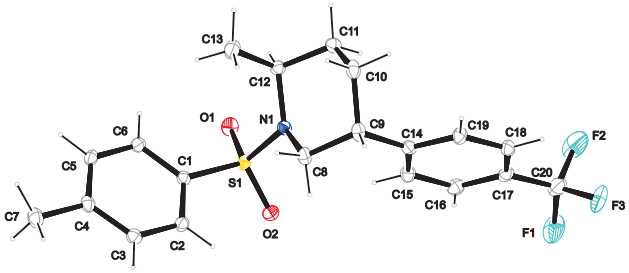
Crystal Data

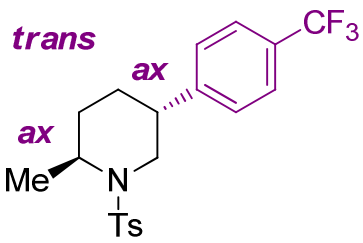
net formula	$C_{20}H_{22}N_2O_2S$
M_r/g mol^{-1}	354.467
crystal size/mm	0.22 × 0.16 × 0.06
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	7.4047(6)
b/Å	9.5212(9)
c/Å	13.7988(11)
α/°	88.074(7)
β/°	76.203(7)
γ/°	87.599(7)
V/Å^3	943.66(14)
Z	2
calc. density/g cm^{-3}	1.24751(19)
μ/mm^{-1}	0.186
absorption correction	'multi-scan'
transmission factor range	0.82353–1.00000
refls. measured	4869
R_{int}	0.0434
mean σ(I)/I	0.1372
θ range	4.29–23.29
observed refls.	1212
x, y (weighting scheme)	0.0470, 0
hydrogen refinement	constr
refls in refinement	2651
parameters	228
restraints	0
$R(F_{obs})$	0.0539
$R_w(F^2)$	0.1174

S	0.831
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.205
min electron density/e Å^{-3}	−0.200

Crystal had poor scattering strength, data collection merely up to a resolution of 0.90 Å.

trans-2-methyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)-piperidine (181ca)





(from Boc-protected piperidine)

Crystal Data

net formula	$C_{20}H_{22}F_3NO_2S$
M_r/g mol^{-1}	397.455
crystal size/mm	0.37 × 0.23 × 0.17
T/K	243(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1/n$
a/Å	10.1552(5)
b/Å	11.7039(5)
c/Å	16.2918(8)
α/°	90
β/°	98.366(4)
γ/°	90
V/Å^3	1915.76(16)
Z	4
calc. density/g cm^{-3}	1.37804(12)
μ/mm^{-1}	0.212
absorption correction	'multi-scan'
transmission factor range	0.94343–1.00000
refls. measured	7447
R_{int}	0.0271
mean σ(I)/I	0.0604
θ range	4.30–26.33
observed refls.	2580
x, y (weighting scheme)	0.0432, 0
hydrogen refinement	constr
refls in refinement	3883
parameters	273
restraints	10
$R(F_{obs})$	0.0368
$R_w(F^2)$	0.0840

S	0.881
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.284
min electron density/e Å^{-3}	−0.379

The F atoms of the CF_3 group are disordered over three sites. A split model has been applied. The sof ratios are 0.83:0.09:0.08. The F atoms on the highest occupied site have been refined anisotropically.

2. Curriculum Vitae

Personal Information

Name	Stephanie Seel
Date of Birth	04.02.1983
Place of Birth	Köln
Citizenship	German

Publications

1.) Seel, S., Thaler, T., Takatsu, K., Zhang, C., Zipse, H., Straub, B. F., Mayer, P. & Knochel, P. Highly diastereoselective arylations of substituted piperidines. *J. Am. Chem. Soc.* **133**, 4774-4777 (2011).

2.) Seel, S., Dagousset, G., Thaler, T., Frischmuth, A., Karaghiosoff, K., Zipse, H. & Knochel, P. Preparation of stereodefined secondary Alkyllithiums. *Chem. Eur. J., accepted.*

Posters

Seel, S., Thaler, T., Takatsu, K. & Knochel, P. "Highly Diastereoselective Arylations of Substituted Piperidines".
16th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (**OMCOS 16**), Shanghai, China. Juli, **2011**.

Seel, S., Dagousset, G., Thaler, T. & Knochel, P. "New Insights into the Stereochemical Behaviour of Secondary Zn- and Li-Organometallics".
4th Symposium of the Sonderforschungsbereich (SFB) 749, Hanns-Seidel-Stiftung, Wildbad Kreuth. März, **2012**.